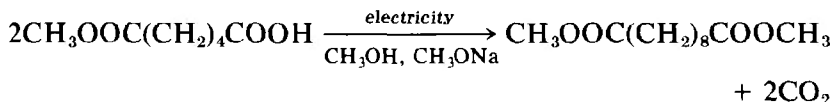


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ANODIC OXIDATION OF ACIDS: DIMETHYL DECANEDIOATE

(Decanedioic acid, dimethyl ester)



Submitted by D. A. WHITE¹

Checked by RONALD F. SIELOFF and CARL R. JOHNSON

1. Procedure

The electrode assembly (Note 1) is constructed; the platinum electrodes are positioned vertically, parallel, and about 5 mm apart by careful bending of the lower platinum wire connections.

To a 500-mL, round-bottomed flask having a central 34/45 standard taper neck and two 24/40 standard taper necks are added 120 g (0.75 mol) of methyl hydrogen hexanedioate (Note 2), 250 mL of methanol, 4.1 g (0.075 mol) of sodium methoxide, 10 mL of pyridine, and a magnetic stirring bar. The electrode assembly is inserted so that the platinum electrodes are immersed in the solution. A thermometer and reflux water condenser are attached. The mixture is heated to 60°C and stirred until the sodium methoxide dissolves.

The mixture is electrolyzed with a constant current of 1.1 A (Note 3) until GLC analysis (Note 4) of the solution shows the absence of the peak due to methyl hydrogen hexanedioate. This requires about 23 hr; electrolysis is continued for an additional 2.5 hr at the same current (Note 5). Throughout the electrolysis the reaction mixture is maintained at 62–65°C by passage of the current. After about 1 hr of electrolysis, when conditions are stabilized, the reaction may be left unattended.

The yellow reaction mixture is allowed to cool and then is acidified with 20 mL of glacial acetic acid. The acidified solution is transferred with methanol washing to a 1-L round-bottomed flask and evaporated (70–80°C, 12 mm) to dryness. The solid residue is

stirred with 500 mL of diethyl ether for 1 hr. Undissolved solids are removed by filtration and the residue is washed twice with 100-mL portions of diethyl ether. The combined filtrate and washings are washed with aqueous sodium carbonate until neutral and then three times with 200-mL portions of water. The ether solution is dried over anhydrous calcium sulfate. Filtration and evaporation of the ether afford a yellow oil that is distilled under a reduced pressure through a Vigreux column (30 × 2.5 cm). This gives 6–7 g of dimethyl hexanedioate (bp 69–71°C, 0.02 mm), 3–4 g of a mixed fraction (bp 72–105°C, 0.02 mm) (Note 6), and 60–61 g (70–71%) of dimethyl decanedioate (bp 105–107°C, 0.02 mm). The dimethyl decanedioate crystallizes on standing at room temperature, mp 26.5–27.2°C (Note 7 and 8).

2. Notes

1. The electrode assembly shown (Figure 1) is fairly versatile and has been used by the submitter in flasks with electrolyte volumes of ca. 40 mL to 4 L. Additionally, the platinum electrodes may be replaced by other electrodes that fit directly into the thermometer adaptor, e.g., commercially available ¼ in. graphite or stainless-steel rods. In the present example the electrodes are positioned vertically and are of opposite polarity. In other cases they may be positioned horizontally (parallel to a mercury cathode) and are both anodic.

The thermometer adaptors are available commercially (Ace Glass Company, Vineland, NJ). The platinum wire to platinum electrode connection was made by laying the wire on the foil, heating both parts to red heat with an oxygen–natural gas flame, and forcing the two together with a sharp hammer blow.

2. Methyl hydrogen hexanedioate (adipic acid, monomethyl ester) was obtained from Aldrich Chemical Company, Inc.

3. The cell voltage, initially 25 V, increased slowly to 27 V. A power supply operating in a constant current mode was used to supply the current. [Since there is little change in cell voltage, a constant voltage power supply capable of delivering 24 V (e.g., two automobile batteries) could also be used.] The cell voltage is important only in connection with the amount of heat generated in the solution by the passage of current. This depends on the product

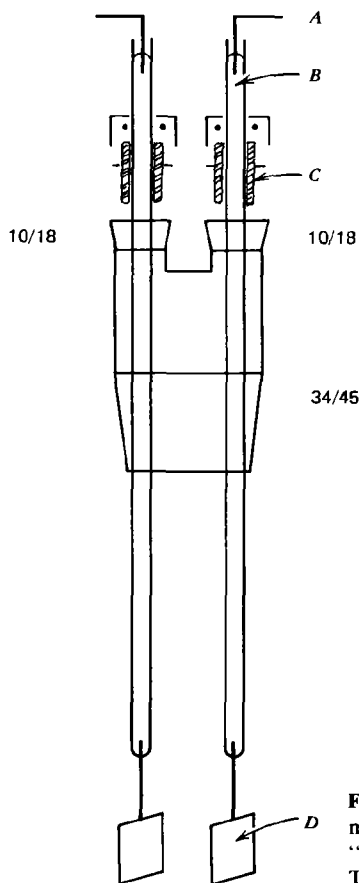


Figure 1. Electrode assembly: (A) platinum wire; (B) mercury-filled 6-mm-o.d. glass tubing; (C) "thermometer" adaptor, 10/18 standard taper joint, Teflon; (D) platinum electrodes 25 × 30 mm.

of current and voltage. The voltage should not be so high that the reflux cannot cope with the heat generated or so low that the reflux temperature is not attained. It should be in the range 20–30 V. If the voltage should not fall within this range, the electrode separation should be adjusted. Decreasing the separation decreases the cell voltage. However, contact of the electrodes should not, of course, occur.

4. The column used was a 6 ft × 1/8 in. stainless-steel column packed with 5% OV17 on 100/120 mesh Chromosorb W. The column temperature was increased at 10°C per minute from 60°C to 260°C.

5. The additional current passed is to allow for the conversion of that portion of the starting material which is converted to the sodium salt by the added sodium methoxide and which is not detected by gas chromatography.

6. The quantity of ester obtained (0.26 mol) theoretically requires 0.52 Faradays. Actual current passed was 28 A-hr (1.05 faradays), corresponding to a current efficiency of 50%.

7. The melting point was determined by remelting the product and allowing it to cool with a thermometer inserted into it. Occasional stirring with the thermometer was necessary to prevent supercooling.

8. The product shows ^1H NMR (CDCl_3) δ : 1.2–1.8 (complex, 12, internal methylenes), 2.28 (4, $\alpha\text{-CH}_2$'s), 3.65 (6, OCH_3 's).

3. Discussion

The present preparation is based on that of dimethyl tetradecanedioate,² with the inclusion of some pyridine into the electrolyte, which has been shown³ to be effective in preventing anode coating. The reaction used is an example of the Crum Brown-Walker reaction⁴ (anodic oxidation of half esters of α,ω -dicarboxylic acids), which is itself an example of the Kolbe reaction (anodic oxidation of carboxylic acids). The latter is a very general reaction, and its scope and mechanism have been recently reviewed.^{5,6} The particular example detailed here has some commercial interest and has been extensively examined. For example, the effects of current density (optimum 0.1–0.4 A/cm²), degree of neutralization (optimum <10%), nature of the base used for neutralization, and the nature of the solvent used have been examined.^{7,8} These optimized results were obtained^{7,8} in a specially constructed cell with an electrode gap of ca. 0.15 mm. To obtain reasonable results with the larger electrode gap used in this example (ca. 5 mm; if the gap is made any smaller, inadvertent contact of the electrodes and short circuiting become a strong possibility) and maintain the cell voltage fairly low (within range of inexpensive power supplies), the current density used (0.14 A/cm²) was kept toward the low end of the desirable range and the degree of neutralization (10%) at the highest value consistent with a good yield. In a small-gap cell a current efficiency of 66% together with a chemical yield of 85% has been obtained⁷ in the same solvent and electrolyte system.

In addition to the route described here, dimethyl decanedioate has been prepared by esterification of decanedioic acid with methanol⁹⁻¹³ or diazomethane,¹⁴ hydrogenation of dimethyl 2,5,8-decatrienedioate,¹⁵ and by thermal decomposition of bis(1-methoxy-1-cyclopentyl)peroxide.¹⁶

The present procedure offers an alternative electrochemical setup to accomplish the Kolbe electrolysis of half esters to that reported earlier for the preparation of dimethyl octadecanedioate.¹⁷ In the present case the apparatus offers general versatility and electrode coating is prevented by an additive (pyridine). In the earlier case periodic current reversal was necessary.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

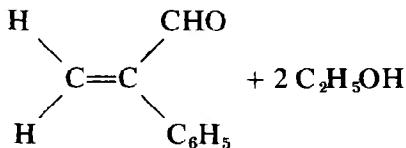
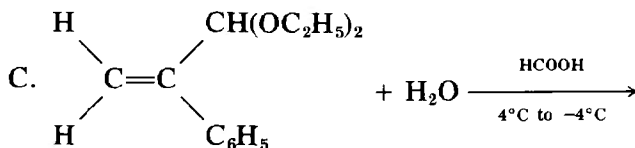
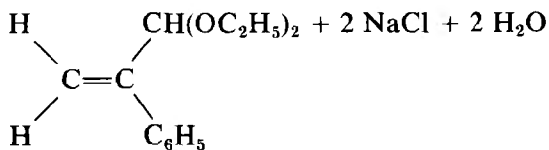
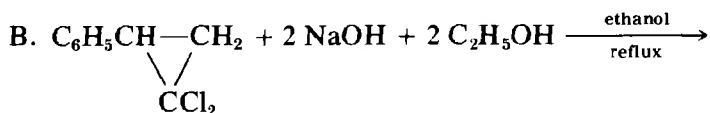
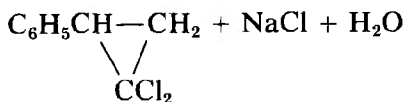
Methyl hydrogen hexanedioate: Adipic acid, monomethyl ester (8); Hexanedioic acid, monomethyl ester (9); (627-91-8)

Dimethyl hexanedioate: Adipic acid, dimethyl ester (8); Hexanedioic acid, dimethyl ester (9); (627-93-0)

Dimethyl decanedioate: Sebacic acid, dimethyl ester (8); Decanedioic acid, dimethyl ester (9); (106-79-6)

ATROPALDEHYDE

(Benzeneacetaldehyde, α -methylene)



Submitted by INGOLF CROSSLAND¹

Checked by THOMAS J. BLACKLOCK and ANDREW S. KENDE

1. Procedure

A. *1,1-Dichloro-2-phenylcyclopropane*. In a 1-L, three-necked, round-bottomed "Morton" flask (Note 1) equipped with a me-

chanical stirrer, a thermometer, and a reflux condenser are placed 57 mL (0.50 mol) of styrene, 50 mL of chloroform, 2 g of triethylbenzylammonium chloride, 25 mL of methylene chloride, and a solution of 77 g of sodium hydroxide in 77 mL of water (Note 2). The mixture is stirred vigorously.

The temperature is allowed to rise to 40°C and then kept between 40°C and 45°C by cooling with water (Note 3). After about an hour evolution of heat subsides, and the dark reaction mixture is heated to 55–60°C for an additional hour. The products are transferred to a 1-L separatory funnel with 250 mL of water and shaken. The organic layer is separated and the aqueous phase extracted with 25 mL of petroleum ether (Note 4). The organic fractions are combined, dried over anhydrous magnesium sulfate powder, filtered, concentrated in vacuo, and distilled through a 20-cm Vigreux column. A forerun at about 50°C (16 mm) consists mainly of styrene. Distillation of the remainder affords 80–82 g (86–88%) of dichlorophenylcyclopropane, bp 118–120°C (16 mm) (Note 5).

B. Atropaldehyde diethyl acetal. A mixture of 18.7 g (0.100 mol) of 1,1-dichloro-2-phenylcyclopropane, 16 g (0.40 mol) of sodium hydroxide, and 160 mL of ethanol is placed in a 250-mL flask fitted with a reflux condenser. The mixture is heated under reflux for 24 hr. Some bumping may occur. Water (200 mL) is added, and the mixture is extracted with three 30-mL portions of petroleum ether. The extracts are combined, dried as above with magnesium sulfate, concentrated in vacuo, and distilled through a 20-cm Vigreux column. The acetal begins to distil at about 70°C (0.5 mm), and the product is collected until the temperature reaches about 100°C. The yield is 14–15 g (68–73%). Gas chromatographic analysis of the product shows it to be about 85% pure (Note 6).

C. Atropaldehyde. The acetal (15 g), placed in a 100-mL flask fitted with a magnetic stirrer and a thermometer, is cooled to about 4°C in an ice bath. A mixture of 15 mL of formic acid and 4 mL of water is similarly cooled and added in one lot with stirring to the acetal. The temperature drops to about –4°C. The homogenous mixture is stirred for 60 sec and then quenched by adding 15 mL of petroleum ether and 25 mL of water. The mixture is transferred to a separatory funnel and thoroughly shaken. The aqueous phase is extracted with two additional 15-mL portions of petroleum ether, and the combined extracts are dried as above with magnesium sulfate and concentrated in vacuo (Note 7). A mixture of 10 mL

each of petroleum ether and diethyl ether is added to the crude aldehyde, and the solution is cooled to about -50°C . After 15 min the colorless crystals are filtered and washed with a few milliliters of the solvent cooled to 0°C . The yield of vacuum-dried product (Note 7) is 5.8–6.8 g (60–70%). Recrystallization from a mixture of 10 mL each of diethyl ether and petroleum ether as above gives 5–6 g, mp $38\text{--}40^{\circ}\text{C}$ (Notes 8 and 9).

2. Notes

1. The checkers used a 1-L, three-necked "Morton" flask² containing deep vertical creases for more efficient mixing and temperature control. The sodium hydroxide solution was added to the stirred reaction mixture through the reflux condenser in one portion. The reaction required only occasional cooling and did not appear to be as highly exothermic during the initial 5 min as stated by the submitter (see Note 3).

2. The submitters used Merck styrene 99%, stabilized with 4-*tert*-butylpyrocatechol. Triethylbenzylammonium chloride was prepared by refluxing equimolar amounts of triethylamine and benzyl chloride in ethanol for 2 hr and removing the solvent in vacuo. The salt is commercially available. The other reagents were technical grade.

3. The reaction can be highly exothermic and it may be a problem to keep the temperature low enough during the first 5 min. A bath with cold water must be kept ready below the flask. Methylene chloride may be added to moderate the reaction.

4. The organic layer is heavier than the aqueous phase. It may be necessary to allow the mixture to stand for an hour before the phases separate.

5. The product shows ^1H NMR (60 MHz, CCl_4) δ : 1.87 (q, 2), 2.83 (triplet, 1), 7.20 (singlet, 5). The reported bp is $118\text{--}119^{\circ}\text{C}$ (16 mm) or 114°C (13 mm).^{3,4} Gas chromatographic analysis indicates the product to be 99% pure, $n_D^{25} 1.551$.

6. The product shows ^1H NMR (90 MHz, CDCl_3) δ : 1.18 (triplet, $J = 7$ Hz, 6), 3.58 (multiplet, 4), 5.22 (singlet, 1), 5.54 (singlet, 2), 7.18–7.58 (multiplets, 5). Minor resonance signals near the foot of the triplet revealed the presence of 1-phenyl-2,2-diethoxycyclopropane as the major by-product. Gas chromatographic analyses on

a 44-m SCOT column, 150–200°C, indicated that the crude product contained the ketal (10%), the starting material (2%), and an unidentified compound (2%). The submitters have not observed polymerization or other deterioration of the crude acetal when it was stored without special precautions in the laboratory for 2 months at ca. 20°C.

7. The aldehyde must be kept cold; see Note 8. If the solution is cooled much below room temperature, crystallization of the aldehyde may take place and render some of the manipulations difficult. The crystals may be dissolved in diethyl ether.

8. The product shows ^1H NMR (90 MHz, CDCl_3) δ : 6.11 (singlet, 1), 6.56 (singlet, 1), 9.72 (singlet, 1), 7.36 (multiplet, 5). Mass spectrum (70 eV, m/e , relative intensity): 132 (M^+ , 51%), 104 (69%), 86 (100%), 78 (13%), 77 (35%). The crystalline aldehyde is unstable at room temperature. When kept for 24 hr in a vacuum-sealed ampoule at 20°C, the crystals slowly deliquesce. The aldehyde may, however, be kept at -6°C for 10 days without any observable deterioration.

9. Procedures B and C work well on a larger scale. Thus atropaldehyde was obtained in 20–26-g quantities from 0.5 mol of styrene (30–39%).

3. Discussion

The method presented here is a simple procedure for the preparation of pure atropaldehyde via its stable acetal, starting from inexpensive chemicals.

The described synthesis of 1,1-dichloro-2-phenylcyclopropane is a slightly modified version of published procedures.^{3,4}

Syntheses of acetals of atropaldehyde have been reported previously, but all required either multistep sequences or difficultly accessible starting materials.^{5,6} Thus the ethylene glycol acetal has been prepared from 2-phenylpropanal in a three-step procedure.⁵ Ring openings of dihalocyclopropanes to give acetals are well known.^{7–10} The reaction of 1,1-dichloro-2-phenylcyclopropane with methanolic sodium methoxide has been shown to give 1-phenyl-2,2-dimethoxycyclopropane.¹¹

The only described preparatively useful route to atropaldehyde is the hydrolysis of the ethylene glycol acetal mentioned above.⁵

The present method is fast and affords labile aldehyde that is pure enough to allow crystallization. None of the conditions suggested by Gorgues for hydrolysis of acetals are satisfactory for the preparation of atropaldehyde.^{12,13}

Formally the reactions amount to an α -formylation of styrene. The homologous aldehyde may be prepared from propenylbenzene.¹⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Atropaldehyde (8); Benzeneacetaldehyde, α -methylene (9); (4432-63-7)

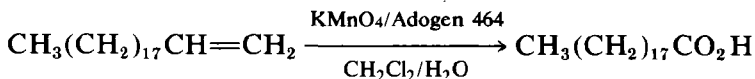
1,1-Dichloro-2-phenylcyclopropane: Benzene, (2,2-dichlorocyclopropyl)- (8,9); (2415-80-7)

Atropaldehyde diethyl acetal (8); 1-Propene, 3,3-diethoxy-2-phenyl- (9); (-)

Pyrocatechol, 4-*tert*-butyl- (8); 1,2-Benzenediol, 4-(1,1-dimethylethyl)- (9); (98-29-3)

1-Phenyl-2,2-diethoxycyclopropane: Benzene, (2,2-diethoxycyclopropyl)- (8,9); (-)

**CARBOXYLIC ACIDS FROM THE OXIDATION OF
TERMINAL ALKENES BY PERMANGANATE:
NONADECANOIC ACID**



Submitted by DONALD G. LEE, SHANNON E. LAMB,
and VICTOR S. CHANG¹

Checked by DENNIS P. LORAH and ANDREW S. KENDE

1. Procedure

A 5-L, three-necked, round-bottomed flask fitted with a mechanical stirrer is placed in an ice bath and charged with 1000 mL of distilled water, 120 mL of 9 M sulfuric acid, 3.0 g of Adogen 464 (Note 1), 20 mL of glacial acetic acid, 1000 mL of methylene chloride, and 50 g of 1-eicosene (Note 2). The solution is rapidly stirred and 80 g (0.544 mol) of potassium permanganate is added in small portions over a 3-hr period (Note 3). Stirring is continued for an additional 18 hr at room temperature. The mixture is cooled in an ice bath, and 60 g of sodium bisulfite is added in small portions to reduce any precipitated manganese dioxide. The solution is acidified, if basic, with sulfuric acid and separated. The aqueous layer is extracted with two 400-mL portions of methylene chloride. The organic extracts are combined, washed with two 400-mL portions of water, washed once with brine, and concentrated to 400 mL on a rotary evaporator. The resulting mixture is heated to dissolve any precipitated product, a small amount of amorphous solid is removed by filtration, and the filtrate is cooled to 0°C. A first crop of white crystals (33–36 g, mp 67–68°C) is collected by suction filtration and washed with a minimum amount of ice-cold methylene chloride. Concentration of the mother liquor to 150 mL, and cooling to 0°C yields a second crop of crystals (7–12 g). The combined products are dissolved, with heating, in 400 mL of methylene chloride and the pale-yellow solution is allowed to cool to room temperature then *slowly* to –10°C. The white crystals (36–37 g) are collected, washed with a small amount of cold methylene

chloride, and dried in vacuum overnight (mp 68–68.5°C, lit² 67–68°C). The yield is 75–77% (Note 4).

2. Notes

1. Adogen 464, a methyl trialkylammonium (C₈–C₁₀) chloride, was obtained from Ashland Chemical Co.

2. Technical 1-eicosene was obtained from the Aldrich Chemical Company, Inc. and used without further purification. Analysis by quantitative catalytic hydrogenation over Pd–C and NMR spectroscopy indicated that it contained about 10% unreactive, saturated hydrocarbon material.

3. Potassium permanganate was “Baker Analyzed” reagent. About 7.5 g was added every 15 min.

4. The yield was calculated by assuming that the starting material contained 90% 1-eicosene (see Note 2).

3. Discussion

Potassium permanganate is the preferred reagent for the oxidative cleavage of carbon–carbon double bonds.³ Because of its low solubility in nonpolar solvents, however, the reactions have traditionally been carried out in polar organic solvent systems. For example, the use of aqueous *tert*-butyl alcohol⁴ and acetic anhydride⁵ for this purpose has been described. An alternative approach involves the use of phase-transfer agents to solubilize permanganate ion in organic solvents and several examples of this approach have been reported.⁶ Although benzene has often been used as the solvent,² it has been observed that methylene chloride is a superior solvent⁷; better yields are obtained and because of its greater volatility it is more easily removed at the conclusion of the reaction. In addition, methylene chloride is more resistant to oxidation by solubilized permanganate. Adogen 464 was used as the phase-transfer agent because the yields compared well with those obtained when other agents⁸ were used and because it is both inexpensive and readily available. The solutions were maintained acidic to neutralize hydroxide ions formed during the reduction of permanganate ($\text{MnO}_4^- + 2\text{H}_2\text{O} \rightarrow \text{MnO}_2 + 4\text{OH}^-$). In the absence of acetic acid the accumulation of base promotes certain side re-

actions and increases the stickiness of the manganese(IV) oxides which precipitate as the reaction proceeds.

The results obtained with a number of other representative terminal alkenes have been summarized in Table I.

TABLE I
PHASE-TRANSFER-ASSISTED PERMANGANATE OXIDATIONS OF TERMINAL ALKENES

Alkene ^a	Product (Yield) ^b	Purification Method	mp or bp (°C) (Ref.)
1-Docosene	Heneicosanoic acid (84%)	Recrystallization (acetone)	72–74° (75,82) ^c
1-Eicosene	Nonadecanoic acid (80%)	Recrystallization (methylene chloride)	68–68.5° (67–68°) ^d
1-Octadecene	Heptadecanoic acid (81%)	Recrystallization (pet. ether)	60–62° (60–61°) ^e
1-Hexadecene	Pentadecanoic acid (84%)	Recrystallization (ethanol–water)	52–53° (53°) ^e
1-Tetradecene	Tridecanoic acid (83%)	Recrystallization (acetone–water)	43–44° (44.5–45.5°) ^e
1-Decene	Nonanoic acid (92%)	Vacuum distillation	109–111°/2.4 mm (121°/4 mm) ^e
1-Octene	Heptanoic acid (70%)	Vacuum distillation	107–108/7 mm (115–116/11 mm) ^e
Styrene	Benzoic acid (96%)	Recrystallization (water)	121–122° (122°) ^e

^aThe alkenes were obtained from the Aldrich Chemical Company, Inc. Purity ranged from 99 to 87%.

^bThe purity of the starting material was taken into consideration in yield calculations.

^c"Handbook of Chemistry and Physics," The Chemical Rubber Co., 52nd ed.

^dReference 2.

^e"Dictionary of Organic Compounds," Eyre and Spottiswoode, 4th ed.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

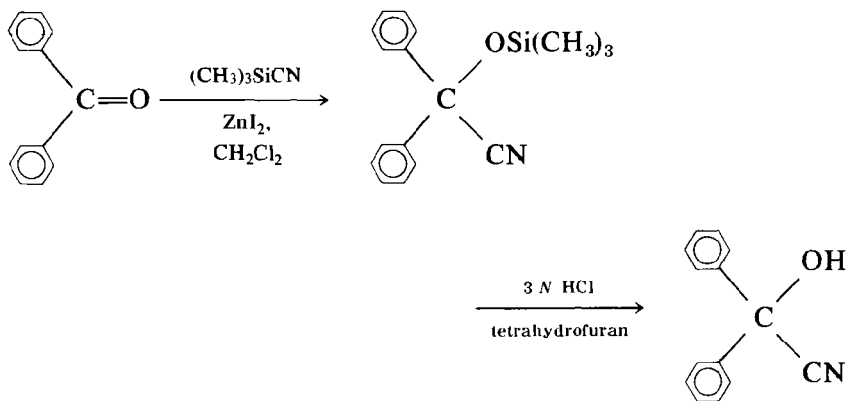
Nonadecanoic acid (8,9); (646-30-0)

Adogen 464 (8,9); (50934-77-5)

1-Eicosene (8,9); (3452-07-1)

CONVERSION OF KETONES TO CYANOHYDRINS: BENZOPHENONE CYANOHYDRIN

(Benzeneacetonitrile, α -hydroxy- α -phenyl)



Submitted by PAUL G. GASSMAN and JOHN J. TALLEY¹
Checked by TOD HOLFER and GEORGE BUCHI

1. Procedure

A. O-(Trimethylsilyl)benzophenone cyanohydrin. A 250-mL, one-necked flask equipped with a reflux condenser, magnetic stirring bar, and drying tube is charged with 22.0 g (0.12 mol) of benzophenone (Note 1), 13.9 g (0.14 mol) of trimethylsilyl cyanide (Note 2), 600 mg (1.9 mmol) of anhydrous zinc iodide (Note 3), and 50 mL of dry methylene chloride (Note 4). The solution is heated at 65°C in an oil bath for 2 hr (Notes 5 and 6). The solvent is removed on a rotary evaporator to yield 36.4–37.9 g of crude product (Note 7), which is used in the next step without purification (Note 8).

B. Benzophenone cyanohydrin. To the 250-mL flask, which contains the crude *O*-(trimethylsilyl)benzophenone cyanohydrin, is added 50 mL of tetrahydrofuran (Note 9), and 30 mL of 3 *N* hydrochloric acid. The mixture is heated at 65°C (oil bath temperature) for 1 hr. The solution is poured into a separatory funnel and 30 mL of water is added. The aqueous phase is separated and back-extracted with three 100-mL portions of diethyl ether. The ethereal extracts are combined with the tetrahydrofuran solution and dried over anhydrous magnesium sulfate, filtered, and the solvent is removed by evaporation on a rotary evaporator to give a yellow solid. The material is recrystallized from 300 mL of toluene and dried at a pressure of 0.05 mm overnight to give 17.7–18.8 g of white crystals. Concentration of the mother liquors to 100 mL produced a second crop of 1.1–3.8 g for a combined yield of 17.9–21.5 g (79–86%), mp 127–130°C (Note 10).

2. Notes

1. Benzophenone was purchased from Distillation Products (Eastman Organic Chemicals) and used without purification.

2. Trimethylsilyl cyanide was prepared shortly before use according to the procedure of Livinghouse, T. *Org. Synth.* **1980**, *60*, 126–131.

3. Anhydrous zinc iodide was purchased from Alfa Products, Ventron Corporation, and used without further purification.

4. The use of this solvent is optional. The reaction can be carried out in the absence of solvent without significant change in

yield. For certain unhindered ketones the solvent is helpful in dissipating the heat generated in the reaction.

5. For certain unhindered ketones external cooling may be necessary instead of heating due to the exothermicity of the reaction.

6. The checkers followed the reaction by IR spectroscopy and found that the benzophenone carbonyl peak (1640 cm^{-1}) disappeared after 2 hr.

7. If purification is desired, it may be achieved by vacuum distillation of this crude product, bp 104°C (0.5 mm).

8. On prolonged standing the crude product appears to undergo some decomposition. Thus it should be used directly in the next step for maximum yield.

9. For many analogs the use of solvent and/or heating is not necessary. However, both solvent and heating are necessary for hindered cyanohydrins, such as the one described in this procedure.

10. The submitters report a melting point of $131\text{--}132.5^{\circ}\text{C}$. The melting point has been previously reported to be $127\text{--}130^{\circ}\text{C}$.²

3. Discussion

Traditionally cyanohydrins have been prepared by processes that require the establishment of an equilibrium between a ketone and its corresponding cyanohydrin. For many ketones, especially those that are sterically hindered, the position of the equilibrium is unsatisfactory for the effective synthesis of the cyanohydrin. We describe herein a general method for the synthesis of cyanohydrins which does not depend on an equilibrium process. As a result this synthetic procedure can be used to convert a wide variety of dialkyl, diaryl, and arylalkyl ketones into their corresponding cyanohydrins. In addition to the described conversion of benzophenone into its cyanohydrin, acetophenone, fluorenone, *tert*-butyl phenyl ketone, and a wide variety of aliphatic ketones have been converted into cyanohydrins by this general procedure (Table I).³

O-(Trimethylsilyl)benzophenone cyanohydrin has been prepared previously by the addition of trimethylsilyl cyanide to benzophenone using an aluminum chloride catalyst.⁴ The preparation of cyanohydrin silyl ethers described in the synthesis is based on

the general procedure of Evans, Carroll, and Truesdale.⁵ Trimethylsilyl cyanide has been prepared also by Zubrick, Dunbar, and Durst.⁶ The overall procedure is that of Gassman and Talley.³

Benzophenone cyanohydrin has been synthesized previously by the nitrogen dioxide oxidation of 1,2-dicyanotetraphenylethane.²

TABLE I
PREPARATION OF CYANOHYDRINS

Product	Yield (%)	mp [bp] (°C)
Cyclohexanone cyanohydrin	90	27–28 [63° (10 ⁻⁶ mm)]
Cyclooctanone cyanohydrin	93	115–116
Fluorenone cyanohydrin	98	118.5–120
<i>tert</i> -Butyl phenyl ketone cyanohydrin	99	82–83
<i>p</i> -Chloroacetophenone cyanohydrin	94	91.5–92.5
<i>p</i> -Nitroacetophenone cyanohydrin	89	112–113
<i>p</i> -Acetylbenzotrile cyanohydrin	95	77.5–78.5
<i>p</i> -Methoxyacetophenone cyanohydrin	96	78–80
<i>p</i> -Methylacetophenone cyanohydrin	97	79.5–80

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

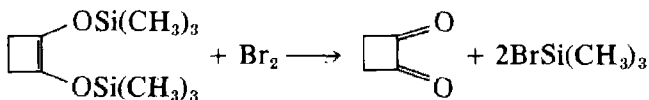
Benzophenone cyanohydrin: Benzeneacetonitrile, α -hydroxy- α -phenyl- (8,9); (4746-48-9)

Benzophenone (8); Methanone, diphenyl- (9); (119-61-9)

O-(Trimethylsilyl)benzophenone cyanohydrin: Benzeneacetonitrile, α -phenyl- α -(trimethylsiloxy)- (8); Benzeneacetonitrile, α -phenyl- α -[(trimethylsilyl)oxy]- (9); (40326-25-8)

Trimethylsilyl cyanide: Silanecarbonitrile, trimethyl- (8,9); (7677-24-9)

1,2-CYCLOBUTANEDIONE



Submitted by J. M. DENIS, J. CHAMPION,
and J. M. CONIA¹

Checked by ROBERT V. STEVENS and STEVEN R. ANGLE

1. Procedure

Caution! This reaction should be carried out in a dark hood to prevent the photoinduced polymerization of the dione.

A 1-L, three-necked, round-bottomed flask equipped with a 500-mL dropping funnel, a nitrogen-inlet tube, a mechanical stirrer, a low-temperature thermometer, and a calcium chloride drying tube is charged with 172 g (0.75 mol) of 1,2-bis(trimethylsiloxy)cyclobutene (Note 1) and 375 mL of anhydrous pentane (Note 2). A dry nitrogen atmosphere is maintained in the system (Note 3) and the solution is cooled to -60°C by means of a dry ice-methanol bath. Then a solution of 120 g (0.75 mol) of bromine and 375 mL of anhydrous pentane is added dropwise with stirring over a period of 2 hr. When the addition is complete, the mixture must be heated to 40°C for 2 hr (Note 4) and concentrated by removing ca. 550 mL of solvent under reduced pressure (15 mm) at room temperature. To isolate the dione the residue is cooled to -60°C by immersion of the flask in a dry ice-methanol bath. The crystallized product is *quickly* filtered through a hermetically sealed (Note 3), 250-mL sintered-glass funnel (porosity 3), a dry nitrogen pressure being used to push down solvent. The

yellow solid is washed with stirring with eight 25-mL portions of anhydrous pentane cooled to -60°C and sucked as dry as possible on the filter. The pentane used in the washing is concentrated under reduced pressure (15 mm) at room temperature to ca. 15 mL, then the flask is again cooled to -60°C . The crystallized product is washed with four 15-mL portions of anhydrous pentane cooled to -60°C as before. The two batches of crystals are of approximately equal purity. The yield of 1,2-cyclobutanedione is 42–46 g (70–73%), mp 65°C (Note 5).

2. Notes

1. The 1,2-bis(trimethylsiloxy)cyclobutene is prepared according to the procedure of Bloomfield.²

2. Pentane is distilled prior to use (bp $36^{\circ}\text{C}/760$ mm) and stored over sodium wire.

3. *Caution! Moisture must be avoided to prevent the ring contraction of the dione into 1-hydroxycyclopropanecarboxylic acid.*²

4. This heating is necessary to complete the reaction.²

5. The yellow product shows in the ^1H NMR (CCl_4) a single signal at 2.98 ppm indicating its high degree of purity. It can be sublimed under vacuum (15 mm) at room temperature, mp 65°C ; IR (CCl_4) cm^{-1} : 1778 and 1810; UV (hexane) nm max (ϵ): 407 (4), 423 (8), 436 (10.5), 453 (19), 463 (17), 489 (42), and 500.5 (28). The dione can be stored at 0°C in a hermetically sealed flask in the dark for months.

3. Discussion

This method of preparation of the 1,2-cyclobutanedione is an adaptation of that independently described by Denis and Conia³ and by Heine.⁴ Acyloins, 1,2-cyclobutanediols, imidazole, thioimidazole, and amino- and cyanofuran derivatives are readily available^{5, 6} from bis(trimethylsiloxy)alkenes.

The bis(trimethylsiloxy)alkene bromination procedure is a large-scale preparation that gives excellent yields of cyclic and acyclic 1,2-diones; however, when enolizable 1,2-diketones are produced, some complications can be encountered.^{7,8}

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Appendix

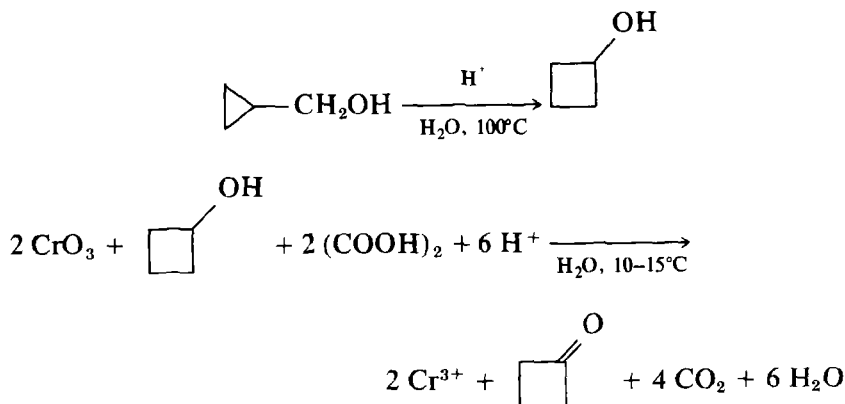
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,2-Cyclobutanedione (8,9); (33689-28-0)

1,2-Bis(trimethylsiloxy)cyclobutene: Silane, (1-cyclobuten-1,2-ylene-dioxy)bis[trimethyl] (8);

Silane, [1-cyclobutene-1,2-diylbis(oxy)]bis[trimethyl] (9); (17082-61-0)

CYCLOBUTANONE



Submitted by MIROSLAV KRUMPOLC and JAN ROCEK¹
 Checked by D SEEBACH, R DAMMANN, F LFHR,
 and M POHMAKOTR

1. Procedure

In a 2-L, three-necked, round-bottomed flask equipped with a reflux condenser are placed 250 mL of water, 48 mL (ca. 0.55 mol) of concentrated hydrochloric acid, and 49.5 g (0.65 mol) of cyclopropylcarbinol (Note 1); the reaction mixture is refluxed for ca. 100 min. The formation of cyclobutanol can be observed nearly instantaneously, as this alcohol is only partially soluble in water and soon separates (Note 2). The flask is then immersed in an ice bath equipped with a mechanical stirrer, a thermometer, and a dropping funnel (using a three-way adapter, parallel side arm), and the reflux condenser is replaced by an ethanol-dry ice trap connected to a U-tube immersed in an ethanol-dry ice bath to ensure condensation of the very volatile cyclobutanone. The flask is charged with an additional 48 mL (ca. 0.55 mol) of concentrated hydrochloric acid in 200 mL of water and 440 g (3.5 mol) of oxalic acid dihydrate (Note 1). The heterogeneous mixture is stirred for ca. 15 min to saturate the solution with oxalic acid. A solution of 162 g (1.62 mol) of chromium trioxide in 250 mL of water is added dropwise with stirring at such a rate that the temperature of the reaction mixture is kept between 10°C and 15°C (NaCl-ice bath, -5°C to -10°C) and the generation of carbon dioxide remains gentle. The reduction of each drop of chromic acid is practically instantaneous. As the addition of the reagent proceeds (1.5-2 hr), oxalic acid gradually dissolves and a dark blue solution containing chromium(III) salts results (Note 3). Just before the end of the oxidation (ca. 10 mL of the chromic acid solution left), the cyclobutanone (with traces of cyclobutanol) trapped in the U-tube (a few milliliters) is added to the reaction mixture. After the oxidation is completed, the ice bath is removed and stirring is continued for ca. 1 hr to bring the reaction mixture to room temperature and to reduce the amount of carbon dioxide in the solution.

The reaction mixture is poured into a 2-L separatory funnel and extracted with four 200-mL portions of methylene chloride (Note 4). The extracts (the lower phase) are combined, dried over anhydrous magnesium sulfate containing a small amount of anhydrous potassium carbonate (to remove traces of hydrochloric acid), and filtered, and the filtrate is concentrated by distillation through a vacuum-insulated silvered column (20-cm length, 1-cm i.d.)

packed with glass helices (size 2.3 mm, Lab Glass, Inc.) and equipped with an adjustable stillhead, until the pot temperature rises to 80°C (Note 5). The crude product is then transferred to a 100-mL flask and distilled through the same column (reflux ratio 10:1) to give 14–16 g (0.20–0.23 mol), 31–35% overall yield (based on pure cyclopropyl carbinol) of cyclobutanone, bp 98–99°C, d_4^{25} 0.926, n_D^{25} 1.4190 (Note 6). The product is sufficiently pure (98–99%) for most purposes (Notes 5, 7, 8, and 9).

2. Notes

1. The following compounds were used as supplied: cyclopropylcarbinol (Aldrich Chemical Company, Inc. or Fluka AG, 95% pure), hydrochloric acid (Fisher Reagent, 36.5–38%), chromium trioxide (Fisher Certified), oxalic acid dihydrate (Fisher Certified), methylene chloride (Fisher Certified).

2. At this point cyclopropylcarbinol has been completely converted into a mixture of products containing ca. 80% cyclobutanol, 8% 3-butene-1-ol, and several additional products observable by GLC analysis in varying amounts. About 95–97% pure cyclobutanol (60–65% yield) can be obtained if the reaction mixture is neutralized with sodium hydroxide and sodium bicarbonate, saturated with magnesium sulfate, extracted with ether, and fractionally distilled on an efficient distillation column. The remaining impurities are extremely difficult to remove.

3. Oxalic acid is used in excess to ensure a rapid oxidation of the alcohol and to destroy the excess chromic acid when the cooxidation process is over. Part of the oxalic acid is consumed by chromium(III) to form oxalatochromium(III) complexes.

4. As cyclobutanone is considerably soluble in water, a thorough and vigorous agitation is recommended to ensure good extraction of the aqueous layer by methylene chloride. Oxalic acid is insoluble in this solvent.

5. The checkers used a silvered, vacuum-insulated column 30 cm in length with 1.5-cm i.d., filled with 4 × 4 mm helices; distillation of CH_2Cl_2 was first done from a 250-mL, two-necked flask with dropping funnel from which the dried extraction solution was continuously added. When ca. 50-mL total volume of solution remained (bath temperature ca. 90°C), it was transferred into a 100-

mL, one-necked flask. Eight fractions of the cyclobutanone were collected at a 15–20:1 reflux ratio: bp/g/% purity of ketone (by VPC): 80–90/1.17/37, 90–95/4.3/53, 95–96/1.71/99.5, 96–97/1.41/—, 96–97.5/1.2/99.9, 97.5–98/3.95/99.9, 98/3.76/100, 98/1.78/99.8. The $n_D^{20.5}$ of fraction 7 was 1.4210.

6. The reported physical constants of cyclobutanone² are bp 99–100°C, d_4^{24} 0.924, n_D^{25} 1.4188.

7. Gas-liquid chromatography [1/8 in. $\times$ 6 ft, 10% diethylene glycol succinate (LAC-728) column, 70°C] of cyclobutanone (99.2% pure) revealed the presence of small amounts of methylene chloride (0.6%) and cyclobutanol (0.2%). No cleavage product, 4-hydroxybutyraldehyde, was found. The traces of water, detected by NMR spectroscopy using CD_3COCD_3 as a solvent, can be removed by drying over molecular sieves.

8. 1H NMR (CCl_4) δ : 1.98, degenerate quintet (2 H, $J = 8$ Hz); 3.03, t (4 H, $J = 8$ Hz). IR (liquid film on KBr plates) cm^{-1} : 1783 (strong, C=O).

9. If the preparation of cyclobutanone from cyclopropylcarbinol is carried out in two steps, with cyclobutanol isolated first, somewhat higher yields can be achieved (70–80% based on cyclobutanol, 45–50% overall yield, purity 98–99%).

3. Discussion

Cyclobutanone has been prepared (1) by pyrolysis of 1-hydroxycyclobutane-1-carboxylic acid³ (15% yield), (2) by reaction of diazomethane with ketene^{4–6} (36% overall yield based on precursors used for the generation of both components⁶), (3) from pentaerythritol, the final step being the oxidative degradation of methylenecyclobutane^{7,8} (30–45% overall yield), (4) by oxidation of cyclobutanol with chromic acid–pyridine complex in pyridine⁹ (no yield is given), (5) by oxidative cleavage of 5,9-dithiaspiro[3.5]nonane, prepared via 2-(ω -chloropropyl)-1,3-dithiane^{10,11} from 1,3-propanedithiol¹² (40% overall yield), (6) via solvolytic cyclization of 3-butyne-1-ol^{13,14} (30% yield), (7) by epoxidation of methylenecyclopropane followed by ring expansion of resulting oxaspiropentane^{15–17} (28% overall yield), (8) from 1,3-dibromopropane and methyl methylthiomethyl sulfoxide via cyclobutanone dimethyl dithioacetal *S*-oxide¹⁸ (75% overall yield), and (9) from 4-

chlorobutyraldehyde cyanohydrin, the final step being hydrolysis of cyclobutanone cyanohydrin¹⁹ (45% overall yield).

The present procedure offers a simple and fast (2–3 days are required) preparation of pure cyclobutanone from cyclopropylcarbinol. The synthesis is carried out in one operation, without isolating the intermediate cyclobutanol. The first reaction, acid-catalyzed rearrangement of cyclopropylcarbinol, has been described by Caserio, Graham, and Roberts.⁹ The novel feature is the preparation of cyclobutanone from cyclobutanol in the presence of oxalic acid. It is based on rapid cooxidation of two substrates proceeding via a three-electron oxidation-reduction mechanism^{20,21} in which chromium(VI) is reduced directly to chromium(III). In the absence of oxalic acid the chromic acid oxidation of cyclobutanol gives along with cyclobutanone ca. 30–40% of 4-hydroxybutyraldehyde,² as the alcohol undergoes extensive carbon–carbon cleavage by chromium(IV).^{2,21,22} The participation of oxalic acid in the reaction process serves to suppress the formation of a chromium(IV) intermediate; the only by-product formed is carbon dioxide.

Cyclobutanone is a versatile starting material used for numerous synthetic and theoretical studies in the chemistry of small rings. The preparation of this compound by the cooxidation process illustrates the synthetic utilization of three-electron oxidation-reduction reactions.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

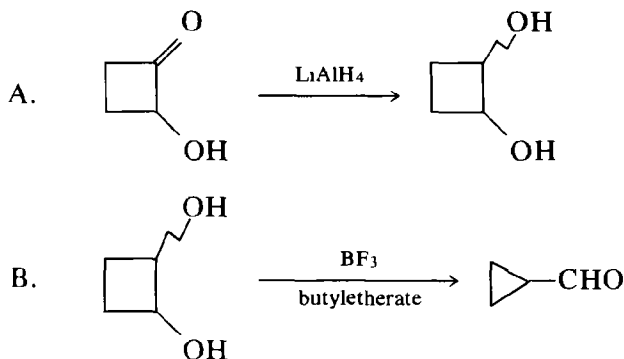
Cyclobutanone (8,9); (1191-95-3)

Cyclopropylcarbinol: Cyclopropanemethanol (8,9); (2516-33-8)

Cyclobutanol (8,9), (2919-23-5)

Oxalic acid dihydrate (8); Ethanedioic acid dihydrate (9); (6153-56-6)

CYCLOPROPANECARBOXALDEHYDE



Submitted by J P BARNIER J CHAMPION
and J M CONIA¹

Checked by ROBERT V STEVENS and STEVEN R ANGLE

1. Procedure

A. *1,2-Cyclobutanediol*. A 2-L, three-necked, round-bottomed flask fitted with a 200-mL dropping funnel, a mechanical stirrer, a nitrogen-inlet tube, and a reflux condenser equipped with a calcium chloride drying tube is charged with 6.2 g (0.16 mol) of lithium aluminum hydride (Notes 1 and 2) and 200 mL of anhydrous diethyl ether (Note 3). The dropping funnel is charged with 42 g (0.48 mol) of 2-hydroxycyclobutanone (Note 4) and 150 mL of anhydrous diethyl ether. While the suspension of lithium aluminum hydride is gently stirred under a nitrogen atmosphere, the solution of 2-hydroxycyclobutanone is added dropwise at a rate maintaining a gentle reflux. When the addition is complete, the mixture is heated at reflux for 1 hr. After the mixture has returned to room temperature, 200 mL of anhydrous diethyl ether is added. The gray reaction mixture is hydrolyzed by addition, in small parts, of a sufficient amount of wet sodium sulfate (Note 5). The reaction mixture is filtered through a sintered-glass funnel (porosity 3). The organic layer is decanted and dried over sodium sulfate. The solid is extracted with anhydrous tetrahydrofuran (Note 6) by means of a Soxhlet apparatus over a period of 24 hr. The combined organic layers are concentrated by distillation of the solvent with a rotary evaporator. The yield of crude *cis*- and *trans*-1,2-cyclobutanediol (ca. 50:50) is 34–40 g (80–95%) (Note 7).

B. *Cyclopropanecarboxaldehyde*. A 50-mL distilling flask equipped with a receiver cooled to -20°C with a dry ice-methanol bath is charged with 34 g (0.39 mol) of a crude mixture of both *cis*- and *trans*-1,2-cyclobutanediol and 10 μL of boron trifluoride butyl etherate (Note 8). The mixture is heated to 230°C with a metal bath. Drops of liquid appear on the condenser, and the aldehyde and water distil into the receiver. The temperature of the distillate oscillates between 50°C and 100°C . Each time the distillation stops, 5–10 μL of boron trifluoride butyl etherate is added to the distilling flask (Note 9). The distillate is transferred into a separatory funnel and sodium chloride is added. The organic layer is decanted and the aqueous layer is extracted three times with 25-mL portions of methylene chloride. The combined organic solution is dried over sodium sulfate, and the solvent is removed by distillation through a 15-cm, helix-packed, vacuum-insulated column. The residue con-

sists of practically pure cyclopropanecarboxaldehyde, 17.5–21.6 g (65–80%) (Note 10).

2. Notes

1. Lithium aluminum hydride is available from Prolabo—France or Alfa Products, Ventron Corporation.

2. On one occasion the checkers found it necessary to add more lithium aluminum hydride (0.3 g) for complete reaction.

3. The checkers used diethyl ether distilled from sodium–benzophenone.

4. The checkers prepared 2-hydroxycyclobutanone by the Bloomfield procedure.² The submitters prepared it by their aqueous hydrolysis procedure.³ This procedure was checked also and proceeds in quantitative yield as described.³

5. Sodium sulfate is mixed with water to form a thick slurry. It is added to the reaction mixture with vigorous stirring to obtain a good dispersion of the slurry in the medium. The added amount of wet sodium sulfate is sufficient when the reaction effervescence ceases and the gray color of the mixture turns to yellow-white.

6. Tetrahydrofuran is purified by distillation from lithium aluminum hydride after 48-hr refluxing over potassium hydroxide (see *Org. Synth.* 1966, 46, 105).

7. The crude 1,2-cyclobutanediol is dried by azeotropic distillation with anhydrous benzene. The product is a mixture of *cis* and *trans* isomers (ca. 50 : 50) readily separable by gas chromatography on a 12-ft column containing 20% silicone SE 30 on Chromosorb W at 140°C. *cis*-1,2-Cyclobutanediol (mp 12–13°C): IR (CCl₄) cm⁻¹: hydroxyl absorption at 3625 and 3580; ¹H NMR (CCl₄) δ: multiplet at 1.98, multiplet at 4.20, and a singlet at 4.51 in a ratio 4 : 2 : 2, respectively. *trans*-1,2-Cyclobutanediol (mp 72°C): IR (CCl₄) cm⁻¹: hydroxyl absorption at 3620; ¹H NMR (CD₃COCD₃) δ: multiplet between 0.9 and 2.2, multiplet between 3.6 and 4.0, and singlet at 3.6 in a ratio of 4 : 2 : 2, respectively.

8. Boron trifluoride butyl etherate, purchased from Fluka AG, is chosen for its convenient boiling point.

9. In a typical run 10 μL of boron trifluoride butyl etherate is added every 10–15 min over a period of 3–4 hr.

10. The crude product is more than 99% pure as shown by gas chromatography; IR (CCl_4) cm^{-1} : carbonyl absorption at 1730; ^1H NMR (CCl_4) δ : doublet at 8.93, multiplet between 1.5 and 2.2, and a multiplet between 1.02 and 1.75 in the ratio 1 : 1 : 4, respectively. The product has bp 95–98°C (760 mm).

3. Discussion

This method of preparation of cyclopropanecarboxaldehyde is an adaptation of that given by J. M. Conia and J. P. Barnier.³ The various methods so far reported, which involve in the last step oxidation,⁴ reduction,⁵ or hydrolysis⁶ of a suitable cyclopropane derivative, are tedious or require expensive starting materials. The other routes involve the direct ring contraction of cyclobutane derivatives into cyclopropanecarboxaldehyde starting from cyclobutene oxide⁷ or from 2-bromo or 2-tosyloxycyclobutanol.⁸ The present procedure uses a particularly easy ring contraction, that of 1,2-cyclobutanediol, and it involves cheap, easily available starting materials. This method can be applied to symmetrical dialkylcyclobutane-1,2-diols, but it gives a mixture of two cyclopropyl carbonyl compounds from unsymmetrical diols.

1. Laboratoire des Carbocycles, Université de Paris-Sud, 91405 ORSAY, France
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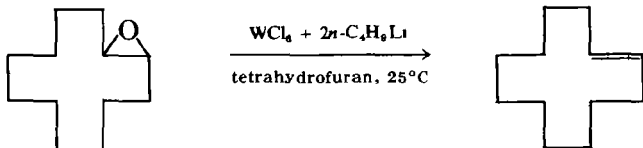
Appendix

Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Cyclopropanecarboxaldehyde (8,9); (1489-69-6)

1,2-Cyclobutanediol (8,9); *cis* (35358-33-9); *trans* (35358-34-0)

2-Hydroxycyclobutanone (8,9); (17082-63-2)

DEOXYGENATION OF EPOXIDES WITH
LOWER VALENT TUNGSTEN HALIDES:
trans-CYCLODODECENE

Submitted by MARTHA A UMBREIT

and K BARRY SHARPLESS¹Checked by RONALD F SIELOFF, MICHAEL F REINHARD
and CARL R JOHNSON

1. Procedure

Caution! Concentrated butyllithium may ignite spontaneously on exposure to air or moisture. Manipulations with this reagent should be performed with great care.

A dry, 1-L, three-necked flask equipped with a thermometer, a mechanical stirrer, and a rubber septum is flushed with nitrogen (admitted through a hypodermic needle in the septum). A nitrogen atmosphere is maintained throughout the subsequent reaction. The flask is charged with 420 mL of tetrahydrofuran (Note 1), and the solvent is cooled to -62°C in an acetone-dry ice bath. Tungsten hexachloride (60 g, 0.15 mol) (Note 2) is then introduced. While the cold suspension is stirred, 31 mL (0.30 mol) of 90% butyllithium in hexane (Note 3) is added slowly from a hypodermic syringe. The rate of addition (complete in ca. 5 min) is such that the temperature remains below -15°C . The resulting mixture is allowed

to warm slowly to room temperature with stirring. The green-brown viscous suspension becomes a dark brown homogeneous solution that eventually turns green at room temperature. Because the reaction with the epoxide is exothermic, the flask is momentarily returned to the acetone-dry ice bath while 14.8 g (0.081 mol) of *trans*-cyclododecene oxide (Notes 4 and 5) is introduced with a hypodermic syringe. The cooling bath is again removed and the reaction mixture is allowed to stir at room temperature. After 30 min (Note 6) the mixture is poured into 600 mL of an aqueous solution that is 1.5 *M* in sodium tartrate and 2 *M* in sodium hydroxide (Note 7), and extracted with 240 mL of hexane. The organic phase is washed with a mixture of 160 mL of water and 80 mL of aqueous saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure with a rotary evaporator. The residual liquid is distilled under reduced pressure, affording 10.5–10.8 g (78–82%) of cyclododecene as a colorless liquid, bp 92–98°C (4.1 mm) (Note 8), 92% *trans* and 8% *cis* by analysis on a ¼ in. × 6 ft GLC column packed with 10% AgNO₃ and 5% Carbowax 20 M on 80–100 mesh Chromosorb W at 110°C.

2. Notes

1. Reagent-grade tetrahydrofuran was freshly distilled from sodium and benzophenone and maintained under nitrogen. In small-scale experiments (1 mmol of tungsten hexachloride in 10 mL of solvent) anhydrous ether was equally effective, but did not give a homogeneous reaction solution.

2. Tungsten hexachloride, purchased from Pressure Chemical Company, was used without further purification. The dark blue-black crystals were pulverized in a dry box or glove bag under a nitrogen atmosphere prior to use. Upon exposure to air or moisture yellow or orange oxides form. Slight contamination from these products does not interfere with the deoxygenation.

3. A suspension of 90% butyllithium in hexane was purchased from Ventron Corporation and was not standardized. The suspension was shaken to obtain uniform density before it was taken up into the syringe. For smaller-scale reactions the submitters report

that 15% (1.6 *M*) butyllithium in hexane or methyllithium in ether is convenient and effective.

4. *trans*-Cyclododecene oxide, purchased from Aldrich Chemical Company, Inc., was used without further purification. The purity of the cyclododecene oxide sold by Aldrich varies, but it is usually >95% *trans*; in this case it was 98% *trans* and 2% *cis* by analysis on a 1/8 in. $\times$ 6 ft. GLC column packed with 3% OV-17 on 80-100 mesh Gas-Chrom Q at 140°C. It is not necessary to wait until the brown solution becomes green before adding the epoxide. After epoxide addition the solution is dark green and appears homogeneous.

5. Molar ratios of tungsten reagent to epoxide of less than 1.5 : 1 resulted in incomplete reaction, while ratios greater than 3 : 1 did not improve, and in some cases actually diminished, the yield of alkene. Ratios of ca. 2 : 1 proved generally effective for a variety of epoxides. Molar ratios of alkyllithium to tungsten hexachloride of less than 2 : 1 also gave incomplete reaction; ratios of 3 : 1 or 4 : 1 are believed to give rise to different reduced tungsten species, which may be used in other reductions.

6. The reaction may be monitored by quenching small aliquots in aqueous 20% sodium hydroxide, extracting into hexane, and analyzing by gas chromatography.

7. Aqueous alkali alone, unless in huge excess, produces an emulsion. The addition of a chelating agent such as tartrate permits a clean separation of phases in a workup of reasonable dimension. A minimum of 6 mol of tartrate and 6 mol of hydroxide per mol of tungsten hexachloride used is adequate to suppress emulsions.

8. An IR spectrum of the product was identical to that of an authentic sample of *trans*-cyclododecene. The PMR spectrum of the product showed the 2 olefinic protons as a multiplet at δ 5.5, the 4 allylic protons as a multiplet at 2.2, and the remaining 16 protons as a peak centered at 1.4.

3. Discussion

This procedure illustrates a general, one-step method to deoxygenate di- or trisubstituted epoxides to olefins in high yield and with high retention of stereochemistry.² Reductions are usually

complete in less than 1 hr at room temperature or below. In certain cases yields and stereochemical retention have been maximized by using 3 equiv of alkyllithium for each equiv of WCl_6 , or by adding LiI .² The reagent is compatible with ethers and esters. It has been used to reductively couple aldehydes and ketones, but considerably longer reaction times and excess reagent are required for appreciable coupling.

Chlorohydrin salts are reduced by the reagent at elevated temperatures and extended reaction times, with complete loss of stereochemistry. Unlike the more highly substituted epoxides, terminal and unsubstituted cyclohexene epoxides appear to proceed, at least in part, via such intermediates, and must be refluxed for several hours to obtain olefins.

Epoxides have been converted to olefins stereoselectively and in good yield by preparation of the iodohydrins, which are then reduced with stannous chloride in the presence of phosphoryl chloride and pyridine.³ A mild, stereoselective epoxide reduction can be achieved with sodium (cyclopentadienyl) dicarbonylferrate, after several *in situ* steps; however, the large steric demands of this reagent limit its use to terminal or very accessible epoxides.⁴ Olefins of inverted stereochemistry have been obtained by the reaction of epoxides with lithium diphenylphosphide and methyl iodide, followed by *cis* elimination of the resulting betaine.⁵ The reduced tungsten reagent complements these methods by reducing the more highly substituted epoxides with retention of stereochemistry. It should be especially useful when iodohydrin formation is sterically impeded or when conditions for the stereospecific iodohydrin reduction are objectionable.

Deslongchamps⁶ and Masamune⁷ have both encountered molecules in which the epoxide moiety was so severely shielded on the backside that any *trans* addition (e.g., iodohydrin formation) was inconceivable. Reduction with the tungsten reagent gave excellent yields of olefin in both cases. Parker employed the tungsten reagent to selectively reduce the trisubstituted epoxides of the trisepoxide of humulene, in effect functionalizing the least reactive double bond of the parent triene.⁸ Masamune and Parker found that other standard reagents for epoxide reduction failed in these cases; Deslongchamps did not try other methods.

A variety of reducing metals,^{3,9} chromous salts,¹⁰ and lower va-

lent iron¹¹ and titanium¹² salts convert epoxides to olefins in one step, but yields are usually low or moderate and stereochemistry is largely or completely lost. Routes involving thionocarbonates,¹³ episulfides,¹⁴ and episelenides¹⁵ have also been used to convert epoxides to olefins. Epoxides activated by adjacent carbonyl, ester, or hydroxy groups have been reduced by special methods.¹⁶

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Appendix

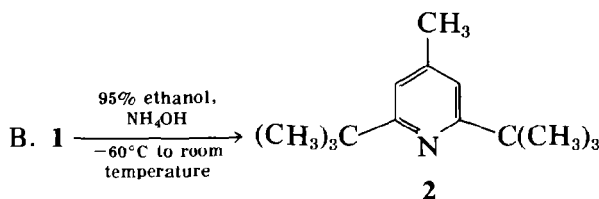
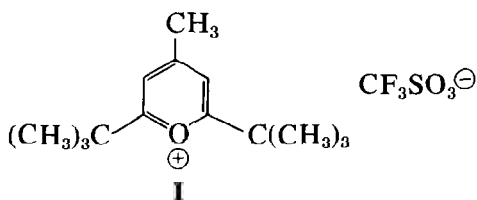
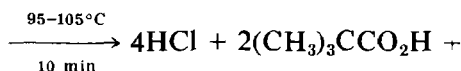
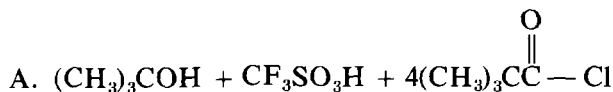
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Tungsten hexachloride Tungsten chloride (WCl₆) (8,9); (13283-01-7)

Trans-Cyclododecene oxide: *trans*-13-Oxabicyclo[10.1.0]tridecane (8,9); (4683-60-7)

Cyclododecene (8,9); (1501-82-2) ((E) – 1486-75-5, (Z) – 1129-89-1)

2,6-Di-*tert*-Butyl-4-methylpyridine
(Pyridine, 2,6-bis(1,1-dimethylethyl)-3-methyl-)



Submitted by ALBERT G. ANDERSON¹ and PETER J. STANG²
Checked by MARK T. DUPRIEST and GEORGE BÜCHI

1. Procedure

Caution! The reaction in Part A should be conducted in a hood, since some carbon monoxide is generated by partial decarbonylation of pivaloyl chloride.

A. 2,6-Di-*tert*-butyl-4-methylpyrylium trifluoromethanesulfonate (**I**). The center neck of a 5-L, three-necked, round-bottomed flask equipped with a thermometer port, magnetic stirrer bar

coated with Teflon[®], and heating mantle is fitted with a 125-mL pressure-equalizing dropping funnel. The two side necks are fitted with 7 cm (diam) $\times$ 27 cm dry ice condensers vented through oil-filled bubblers into traps containing aqueous 1 *N* sodium hydroxide (Note 1). A thermometer is placed in the thermometer port to extend nearly to the bottom of the flask without contacting the stirrer bar. The apparatus is purged with dry nitrogen, the nitrogen flow is stopped, and to the flask are added 300 g (2.5 mol) of pivaloyl chloride and 46 g (0.62 mol) of anhydrous *tert*-butyl alcohol (Note 2). The condensers are charged with isopropyl alcohol–dry ice and, with stirring, the reaction mixture is warmed to 85°C. Heating is discontinued, and the mantle is allowed to remain in place. Then 187.5 g (109 mL, 1.25 mol) of trifluoromethanesulfonic acid is added with stirring during a period of 2–3 min (Note 3). After the addition is complete, the temperature is maintained at 95–105°C for 10 min with the heating mantle. The mantle is removed, and the brown reaction mixture is first allowed to spontaneously cool to 50°C and finally cooled to –10°C with an isopropyl alcohol–dry ice bath. On addition of 1 L of cold diethyl ether (Note 4), a precipitate forms immediately and is collected, washed with three 300-mL portions of diethyl ether, and air-dried on a medium-porosity fritted-glass filter to give 118–137 g (53–62%) of light tan 2,6-di-*tert*-butyl-4-methylpyrylium trifluoromethanesulfonate, mp 153–164°C (Note 5).

B. 2,6-Di-tert-butyl-4-methylpyridine (2). To 119–128 g (0.33–0.36 mol) of crude pyrylium salt in a 5-L, three-necked, round-bottomed flask equipped with a mechanical stirrer is added 2 L of 95% ethanol. The mixture is cooled to –60°C with an isopropyl alcohol–dry ice bath and to the fine slurry is added, with stirring, in one portion 1 L of concentrated (d 0.90) ammonium hydroxide also cooled to –60°C. The yellow reaction mixture is held at –60°C for 30 min, then allowed to warm to –40°C and maintained at that temperature for 2 hr, during which time the slurry dissolves. The mixture is then allowed to spontaneously warm to room temperature (Note 6). The reaction mixture is divided into two portions. Each portion is poured into a 4-L separatory funnel, 1 L of aqueous 10% sodium hydroxide is added, and the mixture is extracted with four 250-mL portions of pentane (Note 7). The extracts from both portions are combined and

washed with 100 mL of saturated aqueous sodium chloride solution. The pentane is removed on the rotary evaporator (Note 8), leaving a residual light yellow oil that is dissolved in 150 mL of pentane and introduced slowly during 20–30 min onto the top of a 40 × 4.5 cm water-jacketed chromatography column (Note 9) containing 300 g of activated alumina (Note 10). After the solution has been added, the column is filled with pentane and a 1-L constant-pressure addition funnel, also filled with pentane, is fitted to the top of the column to provide a slight head pressure. The elution is completed in ca. 90 min. All the pyridine is obtained in the first 2 L of eluant (Note 11). The pentane is removed on the rotary evaporator to yield 62.7–66.3 g (90–93%) of a colorless, odorless oil that solidifies on cooling or standing, mp 31–32°C (Note 12).

2. Notes

1. Since gas evolution at the onset of the reaction is quite vigorous, the operator should check to see that the passage of gas is unobstructed. Gas entering the sodium hydroxide trap should be passed over the solution, not bubbled through it, to guard against the possibility of sodium hydroxide solution being drawn back into the reaction flask.

2. *tert*-Butyl alcohol was obtained from Eastman Organic Chemicals and was used as received. The checkers also used *tert*-butyl alcohol freshly distilled from potassium with equal results. Pivaloyl chloride was obtained from Aldrich Chemical Company, Inc.

3. Trifluoromethanesulfonic acid FC-24 was obtained directly from the manufacturer, Minnesota Mining and Manufacturing Co. (3M), 15 Henderson Dr., West Caldwell, NJ 07006. Adherence to both the time and temperature during the addition is critical for best results.

4. The diethyl ether is conveniently cooled to –10°C by addition of some dry ice.

5. The crude salt darkens somewhat on standing because of further polymerization of impurities, but this does not affect the preparation of the base. It may be further purified by two recrystallizations at –30°C from isopropyl alcohol (8.7 mL per g) to give colorless needles (94% recovery), mp 168–169°C. The salt is not hygroscopic and may be stored indefinitely at room temperature.

It is characterized by NMR $[(\text{CD}_3)_2\text{SO}]$ δ : 1.45 (s, 18 H), 2.72 (s, 3 H), 8.10 (s, 2 H).

6. The submitters state that the reaction may be monitored by the formation of a brilliant yellow intermediate that fades on completion of the reaction.³ The checkers found it most convenient to remove the cold bath and allow the reaction to stir overnight at room temperature. If the reaction is worked up before completion, a yellow impurity is formed which cannot be removed by subsequent chromatography.

7. Phillips Petroleum Company pentane was used as received. Other brands required distillation to remove small amounts of higher-boiling compounds.

8. Ethanol should not be removed by distillation or use of a rotary evaporator since considerable amounts of product codistil with the ethanol.

9. The water-jacketed chromatography column shown in Figure 1 is useful when low-boiling solvents or heat-sensitive compounds are chromatographed. Considerable heat is generated when the pentane solution containing the pyridine is introduced onto the column. This may cause boiling of the pentane and separation of the alumina. A flow of cold water through the jacket avoids separation of the alumina. The column was packed by slowly adding the alumina to the column half filled with pentane.

10. Aluminum oxide, activated, acidic, was obtained from Aldrich Chemical Company, Inc., and used as received.

11. The progress of the elution may be monitored by occasionally spotting a fluorescent TLC plate and examining the plate under short-wave UV light; the pyridine appears as a dark blue spot. Attempts to completely remove colored impurities by distillation, acid-base extraction, or activated charcoal were unsuccessful.

12. Additional physical constants are bp 148–153°C (95 mm), 223°C (760 mm); HPtCl_6 salt mp 213–214°C (decomp), $\text{CF}_3\text{SO}_3\text{H}$ salt mp 202.5–203.5°C (from CH_2Cl_2); NMR (CCl_4) δ : 1.29 (s, 18 H), 2.25 (s, 3 H), 6.73 (s, 2 H); pK_a in 50% ethanol: 4.41⁴ vs. 4.38 for pyridine in the same solvent.⁵ Approximately 0.1% of an impurity, identified by gas chromatography-mass spectrum as 2,6-di-*tert*-butyl-4-neopentylpyridine, is also present; this arises by acid-catalyzed dimerization of isobutylene generated in situ during formation of the pyrylium salt.

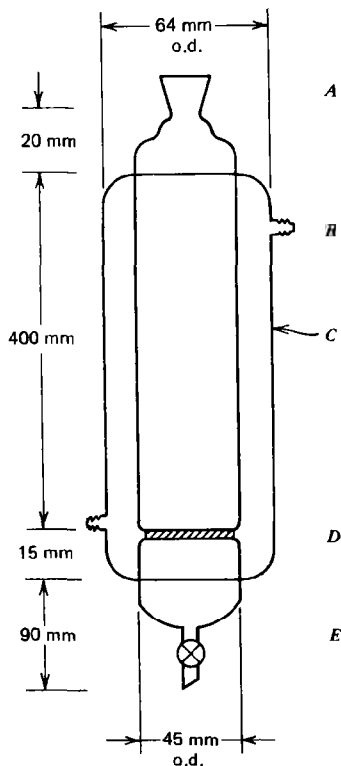


Figure 1. Not drawn to scale. (A) 29/26 joint; (B) hose connection; (C) water jacket; (D) 40 mm Kim-flow fritted disk, size 40-C (coarse), Lab Glass LG28280; (E) Teflon Stopcock 2-mm plug bore, Lab Glass LG9605T.

3. Discussion

2,6-Di-*tert*-butyl-4-methylpyrylium salts have been previously prepared in yields of 4–40% starting with the chloride or anhydride of pivalic acid and employing various counterions, such as ClO_4^- , FeCl_4^- , or AlCl_4^- .⁶ A more recent multistep preparation yields 33% of the perchlorate.⁷ The pyrylium salt has been used to prepare pyrylotrimethinecyanine compounds.⁸ 2,6-Di-*tert*-butyl-4-methylpyridine has been prepared in 44% yield by treating 4-picoline with a 10 molar excess of *tert*-butyl lithium⁴ or by an anionic condensation reaction.⁹ The present procedure is essentially that of Anderson and Stang.³

The pyrylium trifluoromethanesulfonate salt is nonexplosive. The resulting pyridine possesses the ability to distinguish between Lewis and Brønsted acids.^{3,5} It will not react with metal cations¹⁰ or BF_3 . The combination of 2,6-di-*tert*-butyl-4-methylpyridine and methyl trifluoromethanesulfonate results in improved yields under very mild conditions of methylated carbohydrates containing acid- or base-labile groups.¹¹ This pyridine was used as a hindered base in the synthesis of an antigenic bacterial hexasaccharide from *Salmonella newington*.¹² The base has also found use in silylation studies.^{13,14} The hindered pyridine makes possible Friedel-Crafts alkylation of aromatic rings under basic conditions.^{15,16} Substitution of pyridine by the hindered base results in substantially improved yields of a variety of vinyl esters.¹⁶ The use of the sterically hindered base was essential for the preparation of 1-(ethynyl)vinyl trifluoromethanesulfonates.¹⁷ After use the protonated base can be economically recovered in greater than 95% yield by addition of the pyridinium salt to a two-phase mixture of aqueous 50% sodium hydroxide and pentane followed by elution of the pentane solution through an unactivated silica gel column.¹⁷

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Appendix**Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)**

Pivaloyl chloride (8): Propanoyl chloride, 2,2-dimethyl- (9); (3282-30-2)

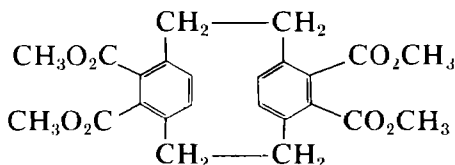
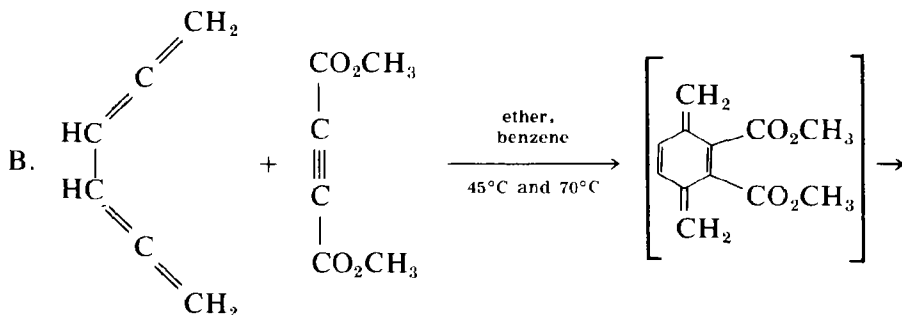
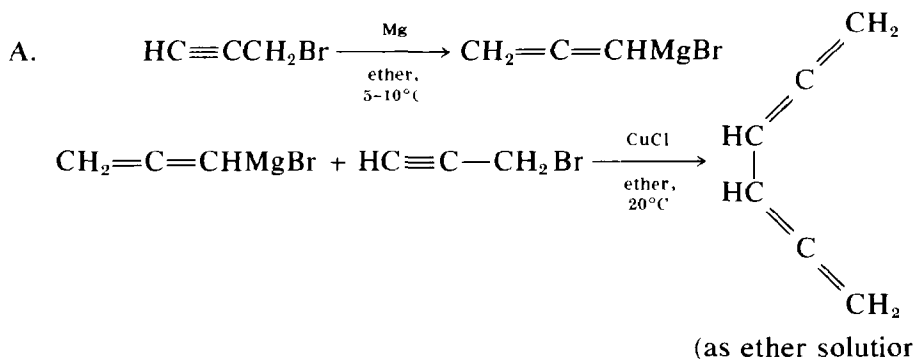
tert-Butyl alcohol (8): 2-Propanol, 2-methyl- (9); (75-65-0)

Methanesulfonic acid, trifluoro- (8,9); (1493-13-6)

Pyridine, 2,6-bis (1,1-dimethylethyl)-3-methyl- (9); (38222-83-2)

**DIELS-ALDER REACTION OF 1,2,4,5-HEXATETRAENE:
TETRAMETHYL[2.2]PARACYCLOPHANE-
4,5,12,13-TETRACARBOXYLATE**

(Tricyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene-5,6,11,12-
tetracarboxylic acid, tetramethyl ester)



Submitted by HENNING HOPF, INGRID BOHM,
and JURGEN KLEINSCHROTH¹

Checked by PAUL F. SHERWIN and ROBERT M. COATES

1. Procedure

Caution! Propargyl bromide is poisonous and should be handled in a well-ventilated hood. For a warning regarding the use of benzene, see Ref. 2.

A. 1,2,4,5-Hexatetraene in ether solution. A 2-L, four-necked, round-bottomed flask is equipped with a mechanical stirrer, a reflux condenser fitted with a drying tube containing anhydrous calcium sulfate (Drierite), a dropping funnel, and a thermometer (Note 1). The flask is charged with 0.5 g (0.002 mol) of mercury(II) chloride and 29.2 g (1.2 mol) of magnesium turnings that have been crushed with a mortar and pestle, and the apparatus is flushed with nitrogen while being heated externally with a Bunsen burner to remove traces of moisture. In the cooled flask are placed 160 mL of anhydrous ethyl ether (Note 2) and 7.6 g (5.0 mL, 0.064 mol) of propargyl bromide (Note 3). The ether begins to reflux within 1 min, indicating that formation of the Grignard reagent has begun (Note 4). The mixture is cooled to 5° in an ice-salt bath and stirred vigorously as a solution of 135 g (89 mL, 1.13 mol) of propargyl bromide in 560 mL of anhydrous ether is added. The addition rate is adjusted so as to maintain the internal temperature between 5°C and 10°C (Note 5). The cooling bath is removed, and the dark green mixture is stirred for 45 min at room temperature (Note 6). A 2-g (0.02 mol) portion of finely pulverized, dry copper(I) chloride (Note 7) is added, and the mixture, which becomes a chocolate-brown color after 2–3 min, is stirred for 15 min at room temperature and cooled again to 5°C with either an ice-water bath or an ice-salt bath. Stirring is continued while a solution of 128 g (85 mL, 1.08 mol) of propargyl bromide in 100 mL of ether is added at a rate such that the internal temperature is kept at ca. 20°C (Note 8). The mixture becomes almost black, and two phases are discernible when the stirrer is stopped, especially toward the end of the addition. The cooling bath is removed, and stirring is continued for 15 min at room temperature to complete the dimerization. The reaction mixture is cooled to 0°C with an ice-salt bath and stirred vigorously as 200 mL of 1 *N* aqueous hydrochloric acid is added (Note 9). The two-phase mixture is warmed to room temperature, and another 100 mL of 1 *N* hydrochloric acid is added. The ether layer is separated and washed with three 100-mL portions of water

(Note 10). A few crystals (0.2–0.5 g) of hydroquinone are added to stabilize the reddish solution, which is then dried with anhydrous potassium carbonate. The drying agent is filtered, and the filtrate is concentrated to a volume of ca. 400 mL by distillation under nitrogen at atmospheric pressure with a 40-cm Vigreux column and a heating bath kept at 40–45°C. The concentrate is purified by vacuum transfer (Note 11), and the now colorless solution, which contains ca. 25–30 g (30–36%) of 1,2,4,5-hexatetraene, is stabilized by adding another 0.1–0.5 g of hydroquinone (Notes 12 and 13).

B. Tetramethyl[2.2]paracyclophane-4,5,12,13-tetracarboxylate. The 1-L flask from Part A containing ca. 25–30 g (0.32–0.38 mol) of 1,2,4,5-hexatetraene in ether solution is equipped with a magnetic stirring bar and a 40-cm Vigreux column for distillation at atmospheric pressure. A solution of 69.4 g (60 mL, 0.49 mol) of dimethyl acetylenedicarboxylate (Note 14) in 220 mL of benzene (Note 15) is added. The resulting solution is stirred and heated at 45°C for 5–7 hr and at 70°C for 20 hr (Note 16). The ether distills slowly at 45°C and rather rapidly at 70°C, the color of the solution changes from yellow to red-orange, and a white solid is gradually deposited. The mixture is cooled and filtered. Recrystallization of the solid from 600–800 mL of toluene affords 27–35 g of white crystalline product, mp 201.5–203°C. The original benzene filtrate and the toluene mother liquor, when evaporated to dryness and crystallized separately from 40–70 mL of toluene, provide 3–4 g and 2–3 g of product, respectively, having essentially the same melting point. The combined yield is 33–41 g (40–50% based on 1,2,4,5-hexatetraene) (Notes 17 and 18).

2. Notes

1. The checkers used a three-necked flask equipped with a Claisen adapter. The straight branch of the adapter was fitted with a thermometer, and the curved branch was mounted with a condenser bearing a nitrogen inlet. After the nitrogen-filled apparatus had been flamed dry and cooled, the dropping funnel was capped with a rubber septum. A nitrogen atmosphere was maintained in the apparatus at all times, and liquids were placed in the dropping funnel via syringe.

2. The checkers dried the ether by distillation from sodium benzophenone ketyl immediately before use.

3. Propargyl bromide may be purchased from Tridom Chemical Inc. and Fluka AG, Buchs, Switzerland. The reagent may also be prepared by the procedure of Gaudemar.³ Propargyl bromide (97%) supplied by Tridom Chemical Inc. was dried by the checkers prior to use by stirring over Linde-type 4A molecular sieves under a nitrogen atmosphere for 2–3 days. The volumetric quantities given in the procedure are for 97% propargyl bromide, which has a density of 1.56 at 20°C according to a catalog from Tridom Chemical Inc.

4. The submitters initiated Grignard formation by adding a few milliliters of a solution of 142.8 g (1.2 mol) of propargyl bromide in 560 mL of anhydrous ether. If the reaction does not begin, they suggest that the flask be heated with a warm stream of air from a "heat gun."

5. The checkers found that the addition time varied from ca. 1 to 4 hr, depending on the temperature of the cooling bath and the extent to which it was stirred.

6. Some unreacted magnesium turnings remain in the flask at this time. However, the submitters recommend against heating the mixture to achieve further conversion, since the initially formed allenylmagnesium bromide will isomerize to 1-propynylmagnesium bromide.

7. The submitters used copper(I) chloride purchased from E. Merck, Darmstadt, which had a greenish tinge attributed to slight contamination by copper(II) salts. The reagent used by the checkers was supplied by J. T. Baker Chemical Company.

8. The checkers, using an ice-salt cooling bath, maintained the internal temperature between 7°C and 12°C. The addition time varied from 15 to 75 min depending on the efficiency of the cooling.

9. The internal temperature was maintained at 10–15°C by the submitters and 5–12°C by the checkers. The time required for the hydrolysis was reduced by the checkers by prior chilling of the hydrochloric acid.

10. Since the product is unstable to oxygen, the checkers tried to keep the ethereal solution under a nitrogen atmosphere during transfers and extractions.

11. The crude solution of 1,2,4,5-hexatetraene may also be employed in part B. However, yields are lower, and the purification of the product becomes tedious owing to the presence of insoluble by-products.

The vacuum transfer may be accomplished with a simple distillation apparatus equipped with a magnetic stirring bar and a 1-L, round-bottomed flask as receiver in the following manner. The crude ethereal solution is chilled to a glass with a liquid nitrogen bath, and the apparatus is evacuated to a pressure of 1–3 mm with a vacuum pump. The apparatus is isolated from the vacuum pump, the cooling bath is removed, and the ether glass is allowed to warm until it becomes mobile. The freeze-evacuate-thaw cycle is repeated two more times to complete the degassing process. The solution is again chilled with liquid nitrogen, the apparatus is evacuated to 1–3 mm, and the system is then isolated from the vacuum pump. The receiving flask is cooled with a liquid nitrogen or dry ice–isopropyl alcohol bath, the cooling bath is removed from the distilling flask, and the ether solution is stirred and allowed to warm to room temperature in the closed system. Once the ether solution becomes mobile, the flask may be warmed cautiously with a water bath at room temperature to speed up the vacuum transfer.

12. Pure 1,2,4,5-hexatetraene polymerizes readily when exposed to air at room temperature. However, solutions of the purified compound are stable for months at 0°C, especially if protected by an inert gas. Contact with air should be minimized to avoid inducing polymerization.

13. The amount of 1,2,4,5-hexatetraene in solution was estimated by the submitters from ¹H NMR spectra and GC analyses. The major product of the dimerization reaction is 1,2-hexadien-5-yne. The submitters have shown that this hydrocarbon does not interfere with the cycloaddition in part B.

14. Dimethyl acetylenedicarboxylate is supplied by Aldrich Chemical Company, Inc.; E. Merck, Darmstadt; and Fluka AG, Buchs, Switzerland. The reagent, bp 110–112°C (15 mm), was distilled before use.

15. The checkers carried out one run on one-tenth scale using toluene instead of benzene in part B. The yield of tetramethyl[2.2]paracyclophane-4,5,12,13-tetracarboxylate, mp

202.5–204°C, was 2.91 g (35% based on 1,2,4,5-hexatetraene in part A).

16. The conditions and isolation procedure given are those used by the checkers. The submitters heated the solution first to 45°C, after which the temperature was gradually increased to 70°C over several hours. The solution was then heated at 70°C overnight, and the solvents were removed by rotary evaporation. The semisolid, yellow-orange residue was recrystallized from benzene or methanol. Concentration of the mother liquor afforded additional crops of crystalline product. The total yield of the tetraester was 25–30 g (30–36% based on 1,2,4,5-hexatetraene), mp 206–207°C.

17. The melting point of the product obtained by the checkers increased only slightly to 202–203.5°C on recrystallization from toluene, benzene, or methanol. The once-recrystallized product was analyzed by the checkers. Analysis calculated for $C_{24}H_{24}O_8$: C, 65.45; H, 5.49. Found: C, 65.51; H, 5.49. The submitters obtained material of analytical purity by sublimation at 180°C (0.001 mm).

The spectral properties of the product are as follows: IR (potassium bromide) cm^{-1} : 1715, 1260, 1195, 1125, 1005, 870; 1H NMR ($CDCl_3$) δ : 2.93–3.43 (nine-line $AA'BB'$ multiplet, 8, two CH_2CH_2), 3.83 (singlet, 12, four CO_2CH_3), 6.80 (singlet, 4, four aryl CH); proton-decoupled ^{13}C NMR ($CDCl_3$) δ (assignment): 33.27 (CH_2), 52.25 (OCH_3), 131.51 (CCO_2CH_3), 134.98 (CCH_2), 139.68 (CH), 168.40 (CO_2CH_3).

18. The submitters have scaled up this procedure to prepare as much as 60 g of the paracyclophane in one run. However, since the volumes of solvents and flasks are quite large, the operations become rather cumbersome.

3. Discussion

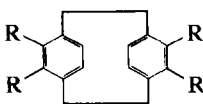
[2.2]Paracyclophanes have been recognized for some time as interesting structures for stereochemical studies and for unusual intra- and intermolecular π -electron interactions.^{4–7} The non-planar, boatlike benzene rings⁸ of these compounds have attracted the attention of numerous synthetic organic chemists^{4–7} as well as theoreticians^{9,10} and spectroscopists.^{7,11}

The principal methods used previously for the preparation of

[2.2]paracyclophanes have been reviewed several times⁴⁻⁷ and include (1) intramolecular Wurtz coupling of appropriately substituted dihalides at high dilution; (2) ring contraction of cyclophanes having larger bridges by sulfone pyrolysis (the most versatile procedure currently known), Stevens rearrangement, and other extrusion reactions; and (3) the dimerization of transient *p*-quinodimethane intermediates (*p*-xylylenes), usually generated from *p*-xylylene precursors by elimination reactions.¹² A *p*-quinodimethane is presumably also formed initially in part B of this procedure. This cycloaddition route to *p*-quinodimethanes and [2.2]paracyclophanes, discovered for the first time in the submitters' laboratories, is attractive on account of the availability of the starting materials, the simplicity of the procedure, and the relatively large quantities of product that may be obtained. The approach appears to be fairly general, since both the bisallene and acetylene components may be varied (Table I).¹³⁻¹⁵ However, methyl 2-butyrate, 2-butyne, diphenylacetylene, and bistrimethylsilylacetylene failed to react with 1,2,4,5-hexatetraene. Another limitation is the exclusive formation of [2.2]paracyclophanes with the *anti* configuration from disubstituted acetylenic dienophiles.

The substituted [2.2]paracyclophanes prepared by the present procedure have proven to be useful starting materials for the synthesis of cyclophanes with extended aromatic ring systems,¹⁶ additional ethano bridges,^{17,18} and chromium tricarbonyl complexes.¹⁹

TABLE I
[2.2]PARACYCLOPHANES PREPARED BY DIELS-ALDER REACTION OF
DISUBSTITUTED ACETYLENES WITH 1,2,4,5-HEXATETRAENE^{13, 14}

	R	mp (°C)	Yield (%)
	CO ₂ CH ₃	203	47
	CO ₂ C ₂ H ₅	133.5	30
	CO ₂ C(CH ₃) ₃	205	20
	CO ₂ H	365 (dec)	5
	CN	320 (dec)	37
	CF ₃	174	21

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,2,4,5-Hexatetraene (8,9); (29776-96-3)

Tetramethyl[2.2]paracyclophane-4,5,12,13-tetracarboxylate: Tri-cyclo[8.2.2.2^{4,7}]hexadeca-4,6,10,12,13,15-hexaene-5,6,11,12-tetracarboxylic acid, tetramethyl ester (8,9); (37437-90-4)

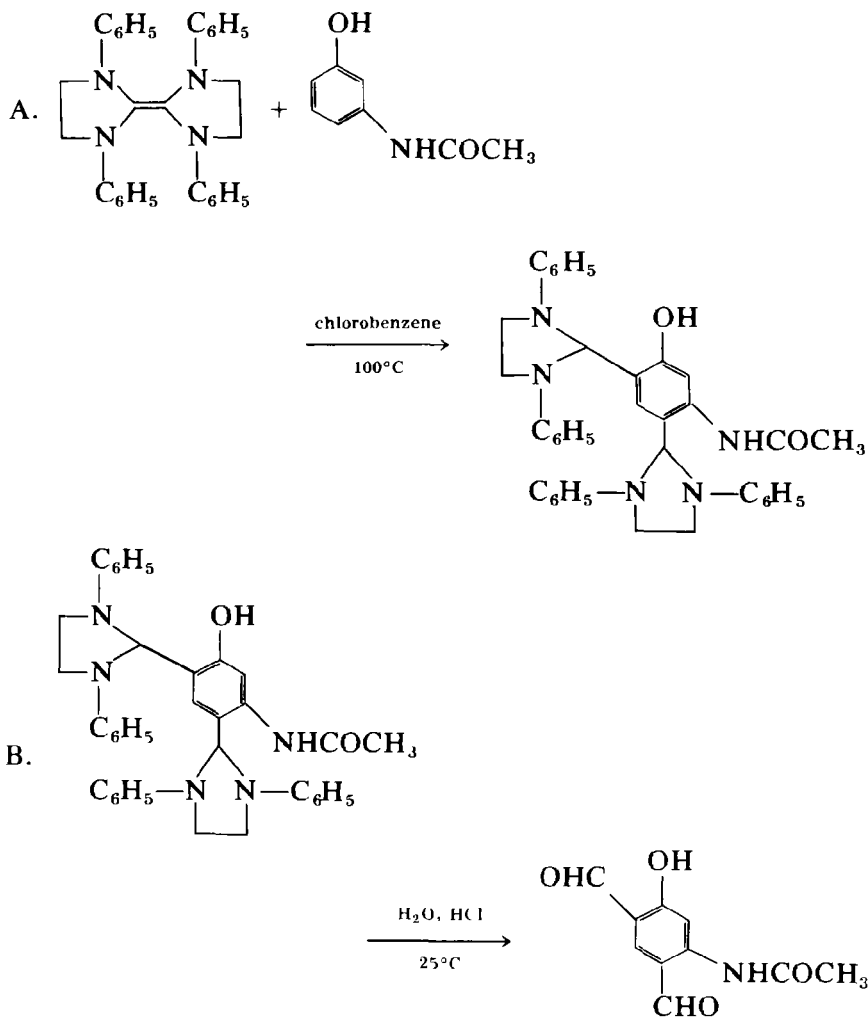
Propargyl bromide: 1-Propyne, 3-bromo- (8,9); (106-96-7)

Dimethyl acetylenedicarboxylate: Acetylenedicarboxylic acid, dimethyl ester (8); 2-Butynedioic acid, dimethyl ester (9), (762-42-5)

1,2-Hexadien-5-yne (8,9); (33142-15-3)

***N*-(2,4-DIFORMYL-5-HYDROXYPHENYL)ACETAMIDE**

(Acetamide, *N*-(2,4-diformyl-5-hydroxyphenyl)-)



Submitted by JURGEN HOCKER and HENNING GIESECKE¹
 Checked by G. SAUCY, HARVEY GURIEN, and GERALD KAPLAN

1. Procedure

A. *N*-[2,4-Bis(1,3-diphenylimidazolidin-2-yl)-5-hydroxyphenyl]acetamide. A 500-mL, 3-necked flask equipped with nitrogen inlet, mechanical stirrer, reflux condenser, and thermometer is charged with 88.8 g (0.2 mol) of 1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene (Note 1) and 30.2 g (0.2 mol) of 3-acetamidophenol (Note 2). The system is flushed with and maintained under nitrogen, and 100 mL of chlorobenzene (Note 3) is added. The suspension is stirred at 100°C for 6 hr (Note 4). 2-Propanol (250 mL) is added to the hot mixture, which is then allowed to cool to room temperature. A pale yellow solid precipitates which is filtered and washed with 200 mL of 2-propanol. Drying in vacuum affords 84.6–93.2 g (71–78%) of *N*-[2,4-bis(1,3-diphenylimidazolidin-2-yl)-5-hydroxyphenyl]acetamide, mp 254–256°C (Note 5).

B. *N*-(2,4-Diformyl-5-hydroxyphenyl)acetamide. A suspension of 95 g of the phenol (prepared under Section A) (Note 6) in 1 L of aqueous 10% hydrochloric acid is stirred for 2 hr at room temperature. The colorless solid (Note 7) is filtered by suction and twice suspended in water at 40°C. Final filtration is followed with a water wash (1 L, 40°C), and the solid is sucked down on the filter. Crystallization from 800 mL of acetonitrile affords 21.8–22.3 g (66–67.5%) of *N*-(2,4-diformyl-5-hydroxyphenyl)acetamide, mp 215–217°C (Note 8).

2. Notes

1. This material was prepared by the procedure of H. W. Wanzlick, *Org. Synth.* **1967**, *47*, 14 or *Org. Synth.* **1973**, *Coll. Vol.* **5**, 115.

2. The checkers purchased 3-acetamidophenol from Aldrich Chemical Company, Inc.

3. The chlorobenzene was dried by azeotropic distillation.

4. The submitters checked the reaction progress by adding chloroform to an aliquot of the reaction mixture and observing it under long-wavelength UV light (350 nm). A bright fluorescence indicated incomplete reaction. The checkers found that further heating

did not eliminate the fluorescence or improve the yield. Adding 1-g quantities of the phenol resulted in quenching of the fluorescence but a lower yield.

5. The product showed the following spectroscopic properties: ^1H NMR (d_7 -DMF) δ : 1.92 (s, CH_3), 3.5–4.1 (m, 8 H, NCH_2), 6.05 (s, 1 H), 6.36 (s, 1 H), 6.5–7.5 (m, 23 H), 9.13 (s, 1 H).

6. The phenol should be ground in a mortar to eliminate lumps.

7. The checkers always obtained pale yellow material.

8. The product had the following spectroscopic properties: IR (KBr) cm^{-1} : 1659, 1644, 1620; ^1H NMR (d_7 -DMF) δ : 2.24 (s, CH_3), 8.22 (s, 1 H), 8.24 (d, $J < 1$ Hz, 1 H), 9.87 (d, $J < 1$ Hz, 1 H), 10.16 (s, 1 H), 11.35, 12.05 (2s, OH, NH).

3. Discussion

The reaction of 1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene with phenols illustrated in this procedure is a general method for the preparation of phenolaldehydes.² Table I gives the aldehydes that have been prepared by conditions similar to those described here.

TABLE I
ALDEHYDES FROM PHENOLS AND 1,1',3,3'-TETRAPHENYL-2,2'-BIIMIDAZOLIDINYLLIDENE

Aldehyde	Yield (%)	
	Imidazolidin-2-yl-phenol	Hydrolysis
4-Hydroxybenzaldehyde	55	88
4-Hydroxy-3,5-dimethylbenzaldehyde	58	80
3-Cyclohexyl-5-methylsalicylaldehyde	43	80
4-Dimethylamino-5-methylsalicylaldehyde	65	54
4-Dimethylaminosalicylaldehyde	52	90
Resorcinol-2,4,6-tricarboxaldehyde	43	96
4-Hydroxy-5-methoxyisophthalaldehyde	55	81
4-Hydroxy-6-methoxyisophthalaldehyde	57	87
Pyrogallol-4,6-dicarboxaldehyde	82	50
8-Hydroxyquinoline-7-carboxaldehyde	76	69

Nitrogen-containing heterocyclic compounds such as indoles and imidazoles are also formylated by the electron-rich olefin. 3-Methylimidazol-5-carboxaldehyde can be prepared from 2-methylimidazole (yield 83%) and 2-phenylindole-3-carboxaldehyde from 2-phenylindole (yield 64%).

The formylation of phenols with the electron-rich olefin to give imidazolidin-2-yl-phenols is very selective and avoids mixtures of *o*- and *p*-isomers which are frequently obtained by methods commonly employed for the synthesis of phenolaldehydes. *Para* substitution of the cyclic aminal group in the phenol is preferred. If the *p*-position is blocked or sterically hindered, the reaction proceeds via the *ortho*-aminals to salicylaldehydes. Incorporation of more than one aldehyde group in the benzene nucleus is often achieved with hydroxy- and aminophenols.

Reaction of phenols bearing strong electron-withdrawing substituents such as dichlorophenols and nitrophenols with 1,1',3,3'-tetraphenyl-2,2'-biimidazolidinylidene results in poor yields. Oxidation of the electron-rich olefin by nitro compounds is also possible.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Acetamide, *N*-(2,4-diformyl-5-hydroxyphenyl)- (8,9); (67149-23-9)

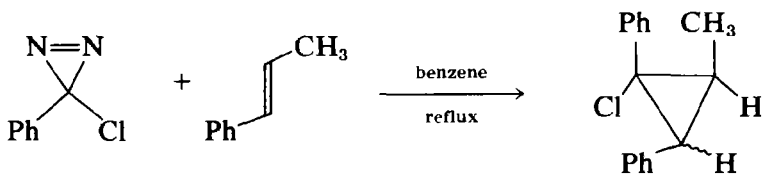
Acetamide, *N*-[2,4-bis(1,3-diphenyl-2-imidazolidinyl)-5-hydroxyphenyl]- (8,9); (67149-22-8)

1,1',3,3'-Tetraphenyl-2,2'-biimidazolidinylidene: $\Delta^{2,2'}$ -Biimidazolidine, 1,1',3,3'-tetraphenyl- (8); Imidazolidine, 2-(1,3-diphenyl-2-imidazolidinylidene)-1,3-diphenyl- (9); (2179-89-7)

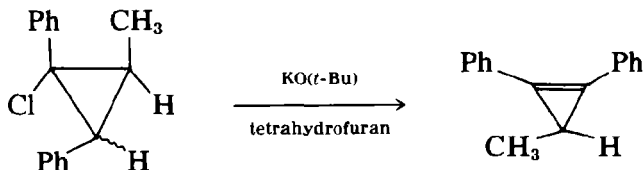
3-Acetamidophenol: Acetanilide, 3'-hydroxy- (8); Acetamide, *N*-(3-hydroxyphenyl)- (9); (621-42-1)

**1,2-DIPHENYL-3-METHYLCYCLOPROPENE:
PREPARATION OF CHLOROPHENYLDIAZIRINE AND
THERMAL GENERATION OF CHLOROPHENYL CARBENE**

(Benzene, 1,1'-(3-methyl-1-cyclopropene-1,2-diyl)-bis-)



(mixture of isomers)



Submitted by ALBERT PADWA, MITCHELL J. PULWER,
and THOMAS J. BLACKLOCK¹

Checked by M. F. SEMMELHACK and A. ZASK

1. Procedure

Caution! Phenylchlorodiazirine is highly explosive (Note 6). It should always be handled with adequate shielding and normal protective equipment such as face shield and leather gloves.

A 3-L, three-necked, round-bottomed flask equipped with a high-speed mechanical stirrer and a 250-mL pressure-equalized dropping funnel is charged with 22.5 g (0.143 mol) of benzamidine hydrochloride (Note 1), 37.5 g (0.62 mol) of sodium chloride, 300

mL of hexane, and 400 mL of dimethyl sulfoxide. The flask is cooled at 0°C in an ice-salt bath (Note 2), and a mixture containing 15.5 g (2.65 mol) of sodium chloride in 1.2 L of aqueous 5.25% sodium hypochlorite solution (Note 3) is added with vigorous stirring over a 15-min period using the dropping funnel. After the addition is complete, stirring is continued for 15 min. At this time the organic phase is separated and the aqueous phase is extracted three times with 75-mL portions of ether. The ethereal extracts are combined with the organic phase and the mixture is washed successively four times with 125-mL portions of water and once with a 125-mL portion of saturated aqueous sodium chloride. The mixture is dried over anhydrous magnesium sulfate and concentrated to a volume of approximately 75 mL at 25°C under aspiration vacuum. The mixture is filtered through a 3 × 14 cm column of silica gel (Note 4) and eluted with 200 mL of anhydrous benzene (Note 5) into a 1-L, single-necked, round-bottomed flask. Concentration under reduced pressure at room temperature to a volume of approximately 50 mL yields a yellow solution (Note 6). The flask is equipped with a magnetic stirrer, heating mantle, and reflux condenser protected from the atmosphere by a calcium chloride drying tube and then charged with 600 mL of anhydrous benzene (Note 5) and 7.49 g (0.0634 mol) of *trans*- β -methylstyrene.

The reaction mixture is then heated at reflux for 3.5 hr and allowed to cool to 25°C. The benzene is removed at 25°C on a rotary evaporator to afford a dark brown oil. This was diluted with 50 mL of ether, filtered through a 3 × 14 cm column of silica gel (Note 4), and eluted with an additional 175 mL of ether. Removal of the ether under reduced pressure yields ca. 21 g of an oily orange solid that consists of a mixture of diastereomeric 1-chloro-1,2-diphenyl-3-methylcyclopropanes (Note 7).

The crude mixture is transferred to a 1-L, one-necked flask equipped with a magnetic stirrer and a calcium chloride drying tube. To the flask is added 450 mL of anhydrous tetrahydrofuran (Note 8), and the mixture is cooled to -78°C in a dry ice-acetone bath. The drying tube is removed for a brief period, and 28.5 g (0.25 mol) of potassium *tert*-butoxide (Note 9) is quickly added in one portion using a powder funnel. The reaction is stirred for 1 hr at -78°C, warmed to 0°C, stirred for 3 hr, and then allowed to

warm to room temperature and stirred for 12 hr. At the end of this time 60 mL of water is added slowly to the reaction mixture. The reaction mixture is concentrated on a rotary evaporator at 25°C to a volume of ca. 150 mL. The mixture is taken up in 160 mL of ether and washed successively with six 60-mL portions of water and one 60-mL portion of saturated aqueous sodium chloride. The ether layer is dried over anhydrous magnesium sulfate, and the solvent is removed under reduced pressure at room temperature. The resulting dark brown oil is chromatographed through a 4 × 41 cm column of silica gel (Note 10) with eluting with hexane. Removal of the solvent under reduced pressure at 25°C affords 10.5–11.5 g (80–88%) of 1,2-diphenyl-3-methylcyclopropene as a pale yellow oil (Note 11).

2. Notes

1. Commercial benzamidine hydrochloride may be used without further purification.

2. Dimethylsulfoxide solidifies on the walls of the container but quickly dissolves on addition of the sodium hypochlorite solution.

3. Any commercial laundry bleach containing 5.25% by weight sodium hypochlorite is suitable.

4. Silica gel of 60-200 mesh was used (35 g).

5. Reagent-grade benzene was distilled from calcium hydride. The first 10% of the distillate was discarded.

6. Alternatively, to isolate the pure phenylchlorodiazirine, distillation through a 3-cm Vigreux column at 25°C (0.1 mm) affords 21.0–23.2 g (48–53%) of a pale yellow oil; IR (cm⁻¹): 3067, 2967, 1706, 1567, 1490, 1437, 1332, 1258, 1200, 1081, 1013, 1001, 905, 758, 692. Foaming may occur during distillation as the residual solvent is removed under high vacuum. A water bath is employed to heat the distillation pot, and at no time should the pot temperature be allowed to rise above 35°C. The distillation receiving flask should be immersed in a cold bath at –60°C to avoid loss of phenylchlorodiazirine.

Phenylchlorodiazirine is reputedly highly explosive and can be detonated by shock and/or elevated temperature.² The authors have encountered one such explosion due to a malfunctioning

water bath thermostat which allowed the pot temperature to rise to 80°C. At this point the distillation mixture detonated. *In the pure form, phenylchlorodiazirine is considerably more shock sensitive than nitroglycerine.*³ Diluted with cyclohexane or benzene, it is not shock sensitive.

7. The ^1H NMR spectrum shows the intermediate chlorocyclopropane to consist of a mixture of two stereoisomers in a 2 : 3 ratio resulting from the nonregiospecific addition of phenylchlorocarbene to *trans*- β -methylstyrene. Crystallization from hexane produced the major isomer as long white needles, mp 98–99°C, which was identified as (*S*)-1-chloro-(*S,S*)-1,2-diphenyl-(*R*)-3-methylcyclopropane; ^1H NMR (CDCl_3 , 100 MHz) δ : 1.6 (d, 3 H, $J = 6.0$ Hz), 2.02 (dq, 1 H, $J = 7.5$ Hz and $J = 6.0$ Hz), 2.44 (d, 1 H, $J = 7.5$ Hz), and 6.6–7.2 (m, 10 H); IR (KBr) cm^{-1} : 3012, 2941, 2899, 2857, 1603, 1580, 1493, 1445, 1383, 1081, 1042, 987, 909, 853, 758, 751, 694. Successive crystallizations to remove the major isomer produced the minor component as a colorless oil identified as (*S*)-1-chloro-(*S,R*)-1,2-diphenyl-(*S*)-3-methylcyclopropane; ^1H NMR (CDCl_3 , 100 MHz) δ : 0.96 (d, 3 H, $J = 6.0$ Hz), 2.02 (dq, 1 H, $J = 7.5$ Hz and $J = 6.0$ Hz), 2.44 (d, 1 H, $J = 7.5$ Hz), and 7.2–7.6 (m, 10 H); IR (neat, cm^{-1}): 3021, 2941, 2924, 1603, 1493, 1449, 1170, 1079, 1044, 1033, 913, 855, 758, 692.

8. Reagent-grade tetrahydrofuran was distilled from lithium aluminum hydride prior to use.

9. Commercial grade potassium *tert*-butoxide (available from MSA Research Corporation, Evans City, PA 16033) was used without further purification.

10. Silica gel (200 g, 60–200 mesh) was used as the adsorbent. The eluant was monitored by thin-layer chromatography with collection of only the first eluted component.

11. Distillation of 1,2-diphenyl-3-methylcyclopropene should not be attempted, as much decomposition occurs. The product is characterized by ^1H NMR (CDCl_3 , 100 MHz) δ : 1.36 (d, 3 H, $J = 5.0$ Hz), 2.18 (q, 1 H, $J = 5.0$ Hz), and 7.1–7.8 (m, 10 H); IR (neat) cm^{-1} : 3049, 3012, 2907, 1815, 1603, 1490, 1370, 1348, 1087, 1073, 1030, 990, 755, 738, 685. 1,2-Diphenyl-3-methylcyclopropene decomposes slowly at 25°C.

3. Discussion

The formation of aryl-substituted cyclopropenes by the addition of phenylchlorocarbene to olefins followed by dehydrohalogenation is a general reaction. The reagent phenylchlorodiazirine decomposes readily to produce phenylchlorocarbene in high yield.⁴⁻⁷ Phenylchlorocarbene adds to many olefins to give halocyclopropanes, which can easily eliminate hydrogen chloride on treatment with base. The reaction of phenylchlorodiazirine with acetylenes produces cyclopropenyl chlorides, which can readily be converted to the corresponding biscyclopropenyl ethers on treatment with aqueous alcohol.^{4,8,9} 1,2-Diphenyl-3-methylcyclopropene has been used to prepare a wide assortment of 1,2-diphenyl-3,3-disubstituted cyclopropenes.^{10,11}

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,2-Diphenyl-3-methylcyclopropene: Cyclopropene, 1-methyl-2,3-diphenyl- (8); Benzene, 1,1'-(3-methyl-1-cyclopropene-1,2-diyl)bis- (9); (51425-87-7)

Chlorophenyldiazirine: 3*H*-Diazirine, 3-chloro-3-phenyl- (8,9); (4460-46-2)

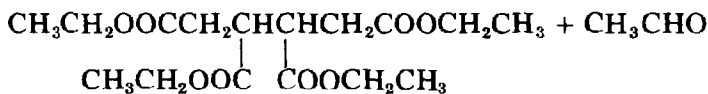
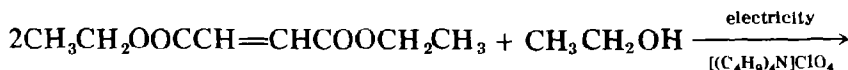
Benzamidine monohydrochloride (8); Benzenecarboximidamide monohydrochloride (9); (1670-14-0)

trans- β -methylstyrene: Benzene, propenyl- (8); Benzene, 1-propenyl- (E)- (9); (873-66-5)

1-Chloro-1,2-diphenyl-3-methylcyclopropane: Cyclopropane, 1-chloro-2-methyl-1,3-diphenyl- (8); Benzene, 1,1'-(1-chloro-3-methylcyclopropane-1,2-diyl)bis- (9); (-)

**ELECTROHYDRODIMERIZATION OF
AN ACTIVATED ALKENE: TETRAETHYL
1,2,3,4-BUTANETETRACARBOXYLATE**

(1,2,3,4-Butanetetracarboxylic acid, tetraethyl ester)



Submitted by D. A. WHITE¹

Checked by CARL R. JOHNSON and DEBRA L. MONTICCILO

1. Procedure

The cell consists of a commercially available four-necked, 500-mL, round-bottomed flask equipped with a 34/45 standard-taper joint electrode assembly (Note 1), a 24/40 standard-taper joint purge and vent assembly, a mercury pool cathode (Note 2), a cathode contact (Note 3), a magnetic stirring bar (Note 4), and thermometer (inserted in a 10/18 standard-taper joint neck). The two platinum anodes of the electrode assembly (Note 1) are positioned in a horizontal plane ca. 1 cm above (Note 4) the mercury (cathode) surface.

To the cell are added diethyl fumarate (172 g, 1.0 mol) (Note 5), absolute ethanol (200 mL), and tetrabutylammonium perchlorate (34.1 g, 0.1 mol) (Note 6). The mixture is allowed to stand for 0.5 hr to allow complete dissolution of the tetrabutylammonium perchlorate. The cell is placed in a flowing-water bath in a hood.

The solution is electrolyzed with continuous magnetic stirring and nitrogen purging at a constant current (Note 7) until the theoretical quantity of electricity ($1.0 F \equiv 1e^-$ per mol diethyl fumarate) has been passed. The rate at which the cooling water in the bath flows is adjusted to maintain the electrolyte solution at 35°C during the first 2 hr of the electrolysis. It is then kept constant for the remainder of the electrolysis. After conditions have stabilized (ca. 1–2 hr of electrolysis), the reaction does not need constant attention, and may be allowed to run overnight.

The reaction mixture is transferred to a 2-L, round-bottomed flask with ethanol washing and the ethanol is removed by rotatory evaporation. Diethyl ether (1 L) is added to precipitate the electrolyte salt, which is collected by filtration and washed with ether. The crude electrolyte is obtained as a white solid (32–32.5 g, theory 34.1 g). The filtrate and washings were combined and evaporated to give a viscous brown oil, which was vacuum distilled through a short Vigreux column (15×2.5 cm). After a forerun of 70 mL of material boiling below 150°C (0.15 mm) the product (92–96 g, 53–56%), bp 150 – 155°C (0.1 mm), is collected (Notes 8 and 9). The forerun contained diethyl maleate, diethyl fumarate, diethyl succinate, and diethyl ethoxysuccinate. The product is a mixture of diastereomers; on standing some meso isomer, mp 74 – 75°C , crystallizes.

2. Notes

1. The electrode assembly has been described (see synthesis of dimethyl decanedioate, p. 1, Note 1 and Figure 1). In this case the electrodes have the same polarity and are electrically connected with a platinum wire dipping into the mercury contacts.

2. About 65 mL (860 g) of mercury was used, giving a pool with a surface diameter of ca. 6 cm.

3. A mercury-filled 6-mm o.d. glass tube with a platinum wire sealed through the lower end was used. The tube was bent to fit the contour of the flask. It was connected to the flask through a 24/40 standard-taper-joint Teflon thermometer adapter (Ace Glass, Vineland, NJ). Contact to the mercury was made with a platinum wire as shown (Figure 1).

4. A 20×0.5 cm Teflon coated stirring bar was used. This thickness (0.5 cm) is close to the maximum usable with an electrode gap of 1 cm. The rate of stirring was the maximum possible without breaking the mercury surface into droplets.

5. Diethyl fumarate, obtained from Aldrich Chemical Company, Inc., was used without prior purification. The submitters used diethyl maleate.

6. Tetrabutylammonium perchlorate, obtained from Eastman Organic Chemicals, was recrystallized from aqueous methanol (75%) and dried in vacuo.

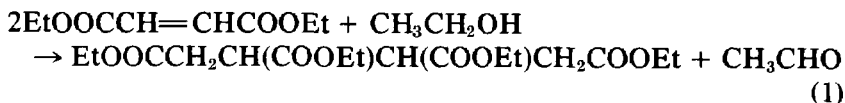
7. The checkers used a Heath Schlumberger Model SP-2711 (30 V, 3 A) power supply at a current of 1.5 A. The cell voltage, initially 25 V, slowly rose to 30 V at the end of the electrolysis and the current dropped to ca. 1 A. The electrolysis required 17–24 hr. The submitters used a current of 1.0 A.

8. The submitters reported a yield of 135 g (78%). In part the reduced yields found by the checkers were caused by mechanical losses during distillation.

9. The product showed ^1H NMR (CDCl_3) δ : 1.25 (t, 12 H, CH_3), ca. 2.6 (m, 4 H, $-\text{COCH}_2$), ca. 3.3 (m, 2 H, CH), 4.2 (two overlapping q, 8 H, OCH_2). Analysis calculated for $\text{C}_{16}\text{H}_{20}\text{O}_8$: C, 55.5; H, 7.6%. Found: C, 55.5; H, 7.8. Molecular weight calculated: 346. Found (osmometrically in CHCl_3): 340, 338.

3. Discussion

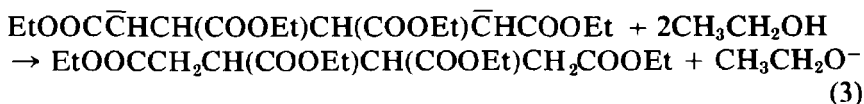
This synthesis is an example of electrohydrodimerization of activated alkenes, the scope and mechanism of which have been recently reviewed.^{2,3} The individual reactions combining to give the overall result



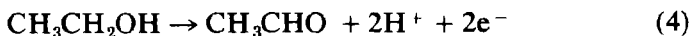
are the cathodic reduction of the alkene to a dimer dianion (in the general case there are two major mechanisms via which the dianion may be formed and these are discussed in the references cited^{2,3}),



the protonation of the dianion by ethanol,

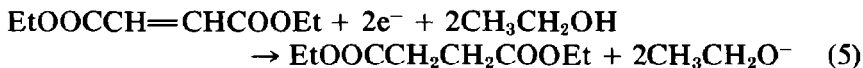


and the anodic oxidation of ethanol.



In addition to providing an anode reaction (a suitable reaction at the "other" electrode is a necessity in any electrochemical reaction), reaction (4) also maintains the pH constant by producing protons to neutralize the ethoxide ions originating from reaction (3).

The present synthesis is an adaptation of a previously reported synthesis⁴ in a divided cell (i.e., separate anode and cathode compartments). The overriding consideration in making this modification has been to simplify the operations involved and render the synthesis more attractive to chemists not well acquainted with electrochemical procedures. The main simplification achieved is that the pH is controlled internally via the anodic generation of protons as noted above (in the reported procedure⁴ this is achieved by periodic addition of acetic acid to the cathode compartment). A further simplification has been to run the reaction with a constant current rather than at controlled cathode potential. After the electrolysis has been initiated, the reaction requires no special attention. A small price is paid for the simplicity of the present synthesis in that the yield is somewhat lower than that obtained previously.⁴ The major by-product formed is diethyl succinate, which results from a $2e^-$ reduction of diethyl fumarate or diethyl maleate:



[cf. (2), which consumes 1e per mol of ester]. The occurrence of reaction (5) leads to incomplete consumption of ester after passage of the theoretical quantity of electricity (there may also be contributions from other sources).

The by-product, diethyl 2-ethoxybutanedioate, may be formed via base-catalyzed reaction in the vicinity of the cathode, where conditions may become quite basic.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

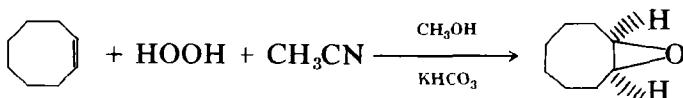
Tetraethyl 1,2,3,4-Butanetetracarboxylate: 1,2,3,4-Butanetetracarboxylic acid, tetraethyl ester (8,9); (4373-15-3)

Diethyl fumarate: Fumaric acid, diethyl ester (8); 2-Butenedioic acid, (E)-, diethyl ester (9); (623-91-6)

Tetrabutylammonium perchlorate (8); 1-Butanaminium, *N,N,N*-tributyl-, perchlorate (9); (1923-70-2)

**EPOXIDATION OF OLEFINS BY
HYDROGEN PEROXIDE-ACETONITRILE:
cis-CYCLOOCTENE OXIDE**

(*cis*-9-Oxabicyclo[6.1.0]nonane)



Submitted by R. D. BACH and J. W. KNIGHT¹
Checked by K. W. FOWLER and G. BÜCHI

1. Procedure

Caution! Organic-soluble peroxides may be explosive (Note 4)!

In a three-necked, 5-L, round-bottomed flask fitted with a mechanical overhead stirrer, addition funnel, and thermometer are placed 484 g (4.4 mol) of *cis*-cyclooctene, 3 L of reagent methanol (Note 1), 330 g (8.04 mol) of acetonitrile, and 77 g (0.77 mol) of potassium bicarbonate (Note 2). To the resulting heterogeneous mixture is added dropwise 522 g (4.6 mol) of 30% hydrogen peroxide with cooling at a rate that maintains the temperature of the reaction at 25–35°C (Note 3). Following the addition of hydrogen peroxide, the ice bath is removed and the reaction mixture is allowed to stir at room temperature overnight. The reaction mixture is divided in half, and each portion is diluted with 500 mL of a saturated sodium chloride solution. Each portion is then extracted with four 500-mL portions of methylene chloride (Note 4). The organic phases are combined, dried over magnesium sulfate, and concentrated at reduced pressure by rotary evaporation. Short-path distillation of the crude product (Note 5) under reduced pressure gives 333–337 g (60–61%) of *cis*-cyclooctene oxide, bp 85–87°C (20 mm), as a white solid, mp 53–56°C (Note 6).

2. Notes

1. Omission of the methanol resulted in substantially reduced yields.

2. The reaction does not proceed well when sodium bicarbonate is used as the base.

3. The reaction is exothermic and caution should be exercised to keep the reaction temperature from rising. The time required for complete addition of the hydrogen peroxide is ca. 2–3 hr. The temperature is maintained at 25–35°C by employing an ice-water bath. When the hydrogen peroxide was added too rapidly, the reaction temperature rose until the solvents refluxed.

4. To check for organic-soluble peroxides, add several milliliters of the methylene chloride solution to a solution containing ca. 1 mg of sodium dichromate, 1 mL of water, and 1 drop of dilute sulfuric acid. A blue color in the organic layer is a positive test for perchromate ion. The checkers found that the combined organic phases exhibited a positive test and therefore stirred them overnight with a solution of 100 g of sodium metabisulfite in 500 mL of water prior to drying.

5. Heat from an IR lamp or heat gun must be applied to the condenser to keep the product from solidifying. The distillation pot should not be taken to dryness because of the possibility of the presence of organic peroxides.

6. The crude product may be used in many cases without further purification. Sublimation of the distilled oxirane affords the product as white needles, mp 56–57°C. The checkers obtained a broader melting point of the distillate, but the product was pure by analytical VPC.

3. Discussion

cis-Cyclooctene oxide has been prepared from *cis*-cyclooctene by the action of perbenzoic acid,² hydrogen peroxide,³ molybdenum hexacarbonyl and *tert*-butyl hydroperoxide,⁴ peracetic acid,⁵ chromic acid,⁶ and polymer-supported peracids.⁷

Oxiranes are typically formed by the action of a peracid such as *m*-chloroperbenzoic acid⁸ on an alkene.⁹ The present method has

the advantage of being useful for both large- and small-scale reactions. The actual epoxidizing agent is generated in situ from the addition of hydrogen peroxide to a nitrile, forming a peroxyimidic acid.¹⁰ This procedure is an adaptation of the method of Payne that utilized an intermediate peroxyimidic acid derived from the reaction of hydrogen peroxide with acetonitrile^{11a} and benzonitrile.^{11b} The alkaline hydrogen peroxide-benzonitrile system has more recently been used with steroids,¹² and in the total synthesis of prostaglandin F_{2α}.¹³ The present method does not require the separation of benzamide from the product. In addition, the reagents are inexpensive and the method is convenient and safe since it does not require large-scale preparation and handling of an organic peracid.

This epoxide has been found to be particularly useful in the laboratory in the large-scale preparation of *trans*-cyclooctene using the procedure of Whitham.¹⁴ *trans*-Cyclooctane-1,2-diol is obtained from *cis*-cyclooctene oxide on treatment with sodium acetate in acetic acid and alkaline hydrolysis of the intermediate *trans*-2-acetoxycyclooctanol. The *trans* diol is converted to its benzaldehyde acetal, which on treatment with butyllithium affords *trans*-cyclooctene in a stereospecific manner.

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Appendix

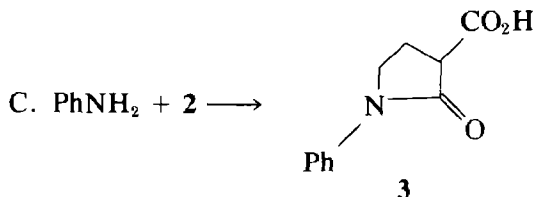
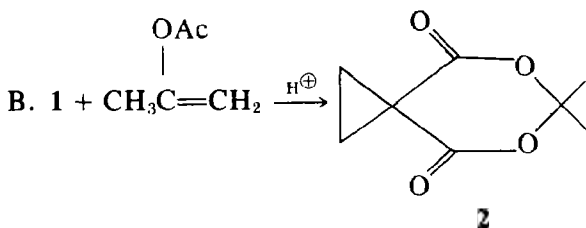
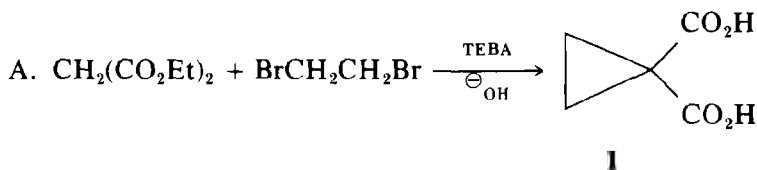
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

cis-Cyclooctene oxide: 9-Oxabicyclo[6.1.0]nonane, *cis*- (8,9); (4925-71-7)

cis-Cyclooctene: Cyclooctene, (*Z*)- (8,9); (931-87-3)

**HOMOCONJUGATE ADDITION OF NUCLEOPHILES
TO CYCLOPROPANE-1,1-DICARBOXYLATE
DERIVATIVES: PREPARATION OF 2-OXO-1-PHENYL-
3-PYRROLIDINECARBOXYLIC ACID**

(3-Pyrrolidinecarboxylic acid, 2-oxo-1-phenyl-)



Submitted by RAJENDRA K. SINGH and SAMUEL DANISHEFSKY¹
Checked by M. R. CZARNY and M. F. SEMMELHACK

1. Procedure

A. Preparation of cyclopropane 1,1-dicarboxylic acid (1). To a 1-L solution of aqueous 50% sodium hydroxide (Note 1), mechanically stirred in a 2-L, three-necked flask, was added, at 25°C, 114.0 g (0.5 mol) of triethylbenzylammonium chloride (Note 2). To this vigorously stirred suspension was added a mixture of 80.0 g (0.5 mol) of diethyl malonate and 141.0 g (0.75 mol) of 1,2-dibromoethane all at once. The reaction mixture was vigorously stirred for 2 hr (Note 3). The contents of the flask were transferred to a 4-L Erlenmeyer flask by rinsing the flask with three portions (75 mL each) of water. The mixture was magnetically stirred and cooled with an ice bath to 15°, and then carefully acidified by dropwise addition of 1 L of concentrated hydrochloric acid. The temperature of the flask was maintained between 15°C and 25°C during acidification. The aqueous layer was poured into a 4-L separatory funnel and extracted three times with 900 mL of ether. The aqueous layer was saturated with sodium chloride and extracted three times with 500 mL of ether. The ether layers were combined, washed with 1 L of brine, dried (MgSO_4), and decolorized with activated carbon. Removal of the solvent by rotary evaporation gave 55.2 g of a semisolid residue. The residue was triturated with 100 mL of benzene. Filtration of this mixture gave 43.1–47.9 g (66–73%) of **1** as white crystals, mp 137–140°C.

B. 6,6-Dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione (2). A suspension of 39.0 g (0.30 mol) of **1** and 33.0 g (0.33 mol) of freshly distilled isopropenyl acetate was vigorously stirred (magnetic stirrer). To this suspension was added dropwise over a period of 30 min, 0.5 mL of concentrated sulfuric acid. While being stirred for an additional 30 min, the solution became clear yellow, and then partly solidified after being kept at 5°C for 24 hr. After addition of 50 mL of cold water, the precipitated solid was filtered, washed with 10 mL of cold water, and air-dried to give 30.9 g of crude spiroacylal **2**. The filtrate was extracted three times with 50-mL portions of ether. The combined organic layers were carefully washed with 50 mL of brine, dried (MgSO_4), and decolorized with activated carbon. Evaporation of the solvent gave an additional 7.8 g of spiroacylal **2** as a yellow solid. The combined samples of

crude spiroacetal (38.7 g) were recrystallized from 110 mL of hexane and 25 mL of benzene to give 28.7–31.5 g (55–61%) of **2** as colorless needles, mp 65–67°C. Concentration of the above mother liquor to ca. 40 mL gave 0.80 g of a second crop of spiroacetal **2** as slightly yellow crystals, mp 58–60°C.

C. Preparation of 2-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (3). To 1.70 g (10 mmol) of spiroacetal **2** was added 2.79 g (3 mmol) of aniline. The mixture became a homogeneous orange solution after 15 min and was allowed to stir at room temperature for 12 hr. The resulting crystalline mass was diluted with 150 mL of chloroform, washed three times with 10 mL of aqueous 10% hydrochloric acid, washed once with 20 mL of brine, dried (MgSO₄), and decolorized with a small amount of activated carbon. Concentration of the organic layer by rotary evaporation gave 5.27 g of a brown residue, which was recrystallized from chloroform–hexane to afford 4.86–5.07 g (79–82%) of the pyrrolidinone **3** as white crystals, mp 146–148°C (dec) (Note 4).

2. Notes

1. Aqueous 50% sodium hydroxide was prepared by dissolving 500 g of sodium hydroxide pellets in water and diluting to 1 L.

2. This compound is commercially available from Aldrich Chemical Company, Inc. Alternatively, it can be made very cheaply and simply by mixing benzyl chloride (1 eq) with triethylamine (2.5 eq). The mixture is allowed to stand for 4–7 days at room temperature. Filtration of the solid and drying in vacuum give triethylbenzylammonium chloride suitable for use in nearly quantitative yield.

3. Some exothermicity results on mixing, causing the temperature to rise to ca. 65°C.

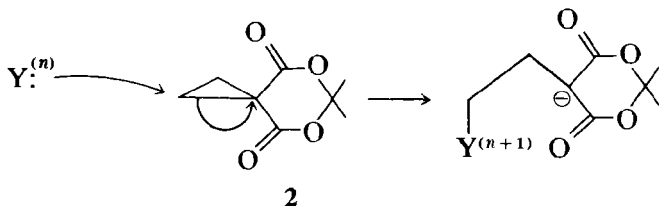
4. At this temperature, after a few minutes, the lactam acid **3** suffers smooth decarboxylation to afford *N*-phenyl-2-pyrrolidinone. Alternatively, the acid can be esterified (methanol–hydrochloric acid), and the resulting 1-phenyl-3-carbomethoxy pyrrolidin-2-one can be used for the introduction of other functionality at the 3-position.

3. Discussion

Previously cyclopropane-1,1-dicarboxylic acid had been prepared²⁻⁴ by hydrolysis of the corresponding diester. The preparation of 1,1-dicarboalkoxycyclopropanes by a conventional double alkylation of diethyl malonate with 1,2-dibromoethane was severely complicated by the recovery of unreacted diethylmalonate. This required a rather difficult distillation to separate starting material and product. In fact, many commercially offered lots of cyclopropane diester contain extensive amounts of diethyl malonate. Furthermore, preparation of the diacid required a separate and relatively slow saponification of the diester.⁵

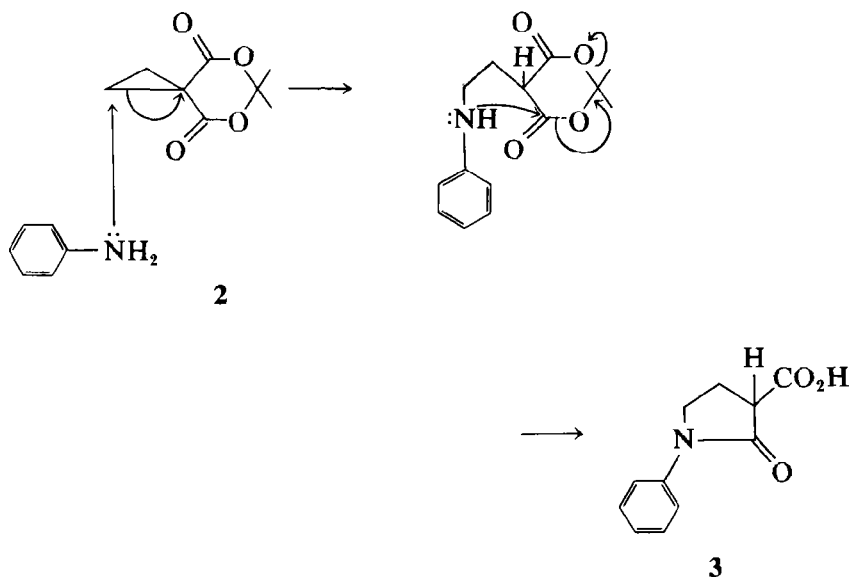
The procedure described here for compound **1** is a scaleup of a published method.⁶ Phase-transfer catalysis⁷ and concentrated alkali are used to effect a one-pot conversion of diethyl malonate to the cyclopropane diacid, which is easily obtained by crystallization. Apparently alkylation of the malonate system occurs either at the diester or monocarboxylate, monoester stage since the method fails when malonic acid itself is used as the starting material. This method of synthesizing doubly activated cyclopropanes has been extended to the preparation of 1-cyanocyclopropanecarboxylic acid (86%) by the use of ethyl cyanoacetate and 1-acetylcyclopropanecarboxylic acid (69%) by use of ethyl acetoacetate.⁶

The spiroacylal **2** is potentially a valuable agent in organic synthesis.⁸ It is readily attacked by a variety of nucleophiles, including pyridine, to give ring-opened products bearing a stabilized carbanion. It is thus seen to be a synthetic equivalent of $^{\oplus}\text{CH}_2\text{-CH}_2\text{-CH(CO}_2\text{H)}_2$ and $^{\oplus}\text{CH}_2(\text{CH}_2)_2\text{-CO}_2\text{H}$, i.e., a homo-Michael acceptor. The general reaction is



Y = aniline, piperidine, pyridine, mercaptide, enolate, etc.

Spiroacetal **2** was designed under the rationale that the constraint of the carbonyl groups into a conformation in which overlap of their π -orbitals with the "bent bonds" of the cyclopropane is assured should dramatically increase the vulnerability of the cyclopropane toward nucleophilic attack.⁸ Experimental support for this notion is abundant.⁸ Spiroacetal **2** is considerably more reactive than 1,1-dicarbethoxycyclopropane in such reactions. For instance, reaction of **2** with piperidine occurs at room temperature. The corresponding reaction in the case of the diester is conducted at 110°C.⁵ Reactions with enolates also occur under mild conditions.⁸ Compound **2** reacts with the weak nucleophile pyridine at room temperature to give a betaine.⁸ An illustrative mechanism for the reaction of the acetal **2** with aniline to afford 2-oxo-1-phenyl-3-pyrrolidinecarboxylic acid (**3**) is



The synthesis of the spiroacetal **2** from the diacid **1** follows a procedure used by Scheuer in a different context.⁹

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1,1-Cyclopropanedicarboxylic acid (8,9); (598-10-7)

Triethylbenzylammonium chloride: Ammonium, benzyltriethyl-, chloride (8); Benzenemethanaminium, *N,N,N*-triethyl-, chloride (9); (56-37-1)

Diethyl malonate: Malonic acid, diethyl ester (8); Propanedioic acid, diethyl ester (9); (105-53-3)

Ethane, 1,2-dibromo- (8,9); (106-93-4)

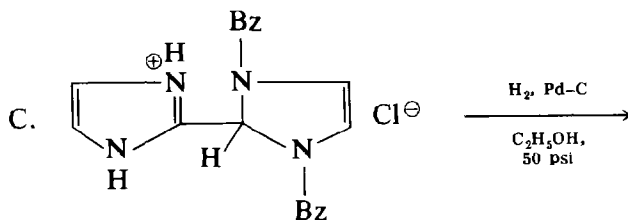
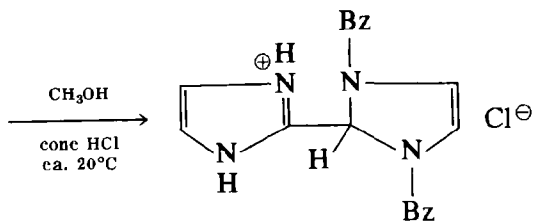
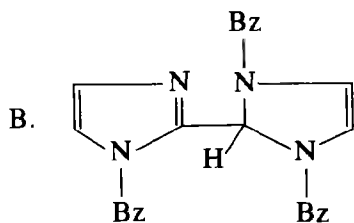
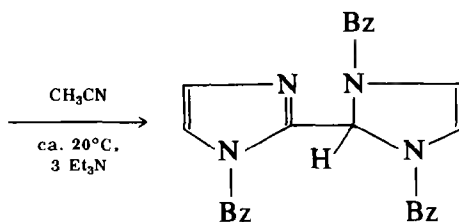
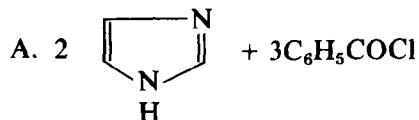
5,7-Dioxaspiro[2.5]octane-4,8-dione, 6,6-dimethyl- (8,9); (5617-70-9)

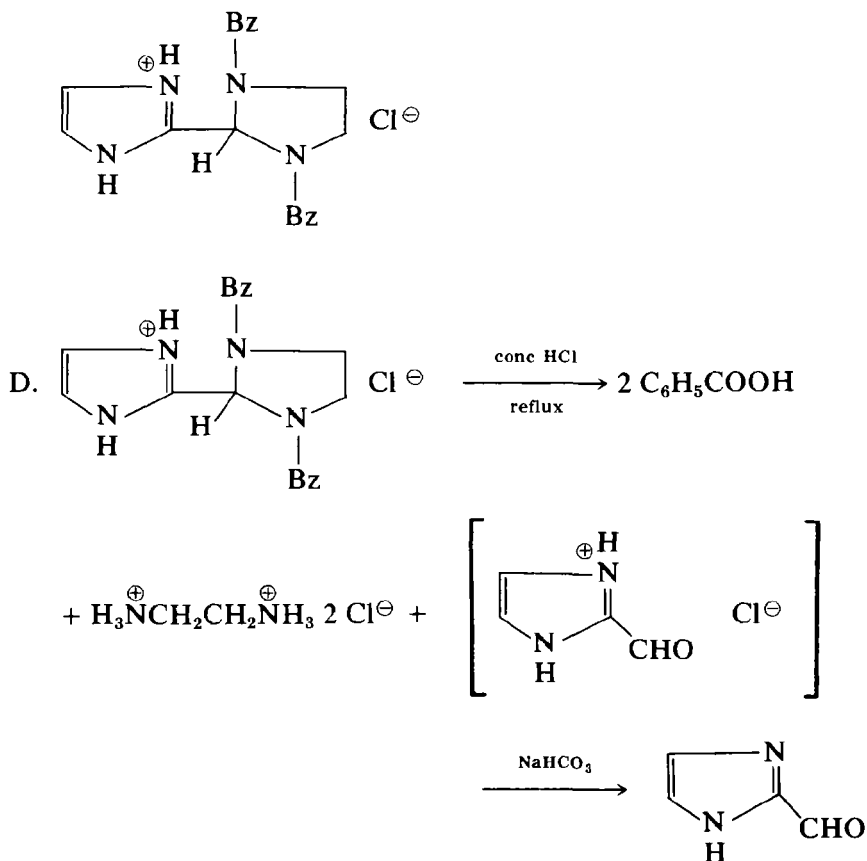
Isopropenyl acetate: Acetic acid, isopropenyl ester (8); Acetic acid, (1-methylethenyl) ester (9); (-)

2-Oxo-1-phenyl-3-pyrrolidinecarboxylic acid: 3-Pyrrolidinecarboxylic acid, 2-oxo-1-phenyl- (8,9); (56137-52-1)

IMIDAZOLE-2-CARBOXALDEHYDE

(1-H-Imidazole-2-carboxaldehyde)





Submitted by LEONARD A. M. BASTIAANSEN, PIETER M. VAN LIER,
and ERIK F. GODEFROI¹

Checked by NANCY ACTON and ARNOLD BROSSI

1. Procedure

A. 1-Benzoyl-2-(1,3-dibenzoyl-4-imidazolin-2-yl)imidazole.² A 12-L, wide-mouthed, round-bottomed vessel fitted with an efficient air-driven stirrer and thermometer is charged with 68 g (1.0 mol) of imidazole (Note 1), 202 g (2 mol) of triethylamine (Note 2), and 1000 mL of acetonitrile (Note 3). To the mixture is added dropwise over a 1-hr period and with external cooling 281 g (2.0 mol) of benzoyl chloride (Note 2); the temperature is maintained at

15–25°C. After addition is complete, stirring is continued for another hour at ambient temperature. With continued stirring 1 L of ether and 5 L of water are introduced, whereupon the temperature is brought to 5°C. The crystalline product is removed by filtration and is sucked dry with the aid of a rubber dam. Rinsing of the filter cake with, successively, water, acetone, and ether gives, on air-drying, 181–190 g (80–85%) of product, mp 197–198°C (Note 4). This product (5 g), taken up in 50 mL of boiling 90% dimethylformamide diluted while hot with water to the cloud point, gives, on cooling, 4.5 g of analytically pure stout prisms, mp 202–203°C (Note 5).

*B. 2-(1,3-Dibenzoyl-4-imidazolin-2-yl)imidazole hydrochloride.*³ Into a 3-L beaker equipped with an air-driven stirrer are successively introduced 150 g (0.335 mol) of dry, unrecrystallized 1-benzoyl-2-(1,3-dibenzoyl-4-imidazolin-2-yl) imidazole, 500 mL of technical-grade methyl alcohol, and 30 mL of concentrated hydrochloric acid. The mixture is stirred as the solids gradually dissolve. After 1 hr a clear yellow solution results, which is allowed to stand for another 5 hr, during which time white solid product begins to precipitate. Technical diethyl ether (1500 mL) is next added, and the mixture is allowed to stand overnight. Filtration and rinsing of the crystals with fresh ether and ultimate air drying furnish 114–119 g (89–93%) of product, mp 238–239°C (Note 6). Analytically pure material, obtained on recrystallizing a small sample from methyl alcohol–ether, has mp 240–241°C.

*C. 2-(1,3-Dibenzoylimidazolidin-2-yl)imidazole hydrochloride.*³ A 1000-mL Paar hydrogenation bottle is charged with 38.0 g (0.10 mol) of dry, unrecrystallized 2-(1,3-dibenzoyl-4-imidazolin-2-yl)imidazole hydrochloride suspended in 300 mL of 95% reagent-grade ethyl alcohol. Then 2 g of 10% palladium on carbon (Note 7) is cautiously added (Note 8). The reaction vessel is now attached to the Paar hydrogenator and, after alternate evacuation and flushing with hydrogen gas, is shaken under a 50 psi atmosphere of hydrogen. Gas uptake ceases after absorption of 1 mol-eq per mol of substrate; this requires ca. 2 hr. The catalyst is removed by vacuum filtration through Hyflow, the filter cake is rinsed with three portions of 95% ethyl alcohol (Note 9), and the filtrate is stripped to leave solid, impure product. This is triturated with 200 mL of ice-cold acetone; filtration and rinsing of the solids with

fresh acetone and ultimately with ether yield 33.2–35.8 g (87–94%) of air-dried material, mp 225–226°C (Note 10). An analytically pure sample from isopropyl alcohol–ether melts at 225–226°C.

*D. Imidazole-2-carboxaldehyde.*³ A solution of 19.1 g (0.05 mol) of dry, unrecrystallized 2-(1,3-dibenzoylimidazolidin-2-yl) imidazole hydrochloride in 200 mL of concentrated hydrochloric acid is refluxed for 22 hr (Note 11). The mixture is then chilled on ice, causing deposition of benzoic acid, which is removed by filtration (Note 11). The filtrate, on evaporation, leaves a residue that is first digested with 100 mL of 95% ethyl alcohol and then cooled on ice. The remaining solids are essentially pure ethylenediamine dihydrochloride and are filtered off (Note 12). Filtrate solvent is again removed under reduced pressure to leave solid residue. This is dissolved in 40 mL of water. Addition of solid sodium bicarbonate until foaming ceases causes imidazole-2-carboxaldehyde to crystallize. The mixture is chilled on ice, and the product is filtered off and washed with ice-water to give, after thorough drying, 3.2–3.7 g (67–77%) of beige crystals, mp 206–207°C. Analytical material, prepared from water, has mp 206–207°C (Note 13).

2. Notes

1. Imidazole is a bulk chemical available from the Badische Anilin- & Sodafabrik AG, 6700 Ludwigshafen/Rhein, West-Germany. The checkers used Aldrich imidazole, 99%, from Aldrich Chemical Company, Inc., 940 W. Saint Paul Ave., Milwaukee, WI 53233.

2. Triethylamine and benzoyl chloride, both 99.5% pure, were purchased from Fluka AG, 9476 Buchs, Switzerland. The checkers used material from Aldrich Chemical Company, Inc.

3. Acetonitrile, 99%, was obtained from Aldrich-Europe, B-2340 Beerse, Belgium.

4. Observing the theoretical stoichiometry, i.e., 2 eq of imidazole and 3 eq each of benzoyl chloride and triethylamine, resulted in significantly lower product yields.

5. The ¹H NMR spectrum (CDCl₃) corresponded to that in the literature²: δ 6.43 (s, 2, vinyl protons), 7.07 (t, 2, imidazole protons), 8.05 (s, 1, methine proton). Analysis calculated for C₂₇H₂₀N₄O₃: C, 72.31; H, 4.49; N, 12.49. Found: C, 72.27; H, 4.54; N, 12.53.

6. The checkers obtained variable melting points that were accompanied by decomposition and depended on the rate of heating. ^1H NMR (CD_3OD) δ : 6.57 (s, 2), 7.50 (m, 13, aromatic protons). Analysis calculated for $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_2 \cdot \text{HCl}$: C, 63.07; H, 4.56; N, 14.71. Found: C, 63.02; H, 4.60; N, 14.79.

7. Merck-Schuchardt "Hydrierkatalisator," purchased from E. Merck, Postfach 4119, 6100 Darmstadt, West-Germany. The checkers used Pd/C from Alfa Products, Ventron Corporation, P.O. Box 299, Danvers, MA 01923.

8. Direct introduction of a dry hydrogenation catalyst into an alcoholic system has been known to bring about spontaneous ignition. This risk may be obviated by addition of a slurry of 2.0 g of catalyst in 15 mL of water to the substrate in 285 mL of absolute ethyl alcohol.

9. Filter cakes of fresh, spent hydrogenation catalysts are known to be pyrophoric and should not be sucked completely dry.

10. The checkers obtained an oily foam that remained oily on adding cold acetone. The oily material became solid on adding and evaporating benzene (2×100 mL). The checkers obtained variable melting points accompanied by decomposition. ^1H NMR (CD_3OD) included an AA'BB' system centered around δ 4.17 (4, CH_2CH_2). Analysis calculated for $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_2 \cdot \text{HCl}$: C, 62.74; H, 5.00; N, 14.64. Found: C, 62.96; H, 4.98, N, 14.42.

11. Benzoic acid sublimes into the condenser and will plug a small-bore condenser.

12. The benzoic acid and ethylenediamine dihydrochloride isolated after the cited reaction time amount to ca. 90%.

13. Imidazole-2-carboxaldehyde has been reported to melt at 204°C ,⁴ $195\text{--}205^\circ\text{C}$,⁵ 195°C ,⁶ 202°C ,⁸ and $190\text{--}196^\circ\text{C}$.⁷ The material prepared has an ^1H NMR spectrum corresponding to that of the literature⁸: δ 7.43 (s, 2, imidazole protons), 9.67 (s, 1, CHO). Analysis calculated for $\text{C}_4\text{H}_4\text{N}_2\text{O}$: C, 49.99; H, 4.19; N, 29.16. Found: C, 50.05; H, 4.26; N, 28.96.

3. Discussion

Synthesis of imidazole-2-carboxaldehyde has previously been reported by manganese dioxide oxidation of the corresponding carbinol,⁴ by acid-promoted cyclization of *N*-(2,2-diethoxyethyl)-2,2-

diethoxyacetamidine,⁵ and by methods centering around formylation of appropriately protected 2-imidazolelithium reagents.^{6,7} The present method constitutes an optimization of the route recently reported from our laboratories.³ Inexpensive, commercially available bulk chemicals are utilized to give imidazole-2-carboxaldehyde via high-yield processes mostly in open vessels and at ambient temperatures. All products are isolated directly from the reaction mixtures in a high state of purity without resorting to extractions, distillations, or recrystallizations. The by-products, benzoic acid and ethylenediamine dihydrochloride, are recovered in nearly quantitative yields. Waste and environmental pollution are kept to a minimum.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Imidazole-2-carboxaldehyde (8); 1*H*-Imidazole-2-carboxaldehyde (9); (10111-08-7)

1-Benzoyl-2-(1,3-dibenzoyl-4-imidazolin-2-yl) imidazole: 2,2'-Bi-1*H*-imidazole, 1,1',3-tribenzoyl-2,3-dihydro- (8,9); (62457-77-6)

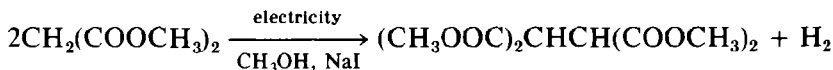
Imidazole (8); 1*H*-Imidazole (9); (288-32-4)

2-(1,3-Dibenzoyl-4-imidazolin-2-yl) imidazole hydrochloride: 2,2'-Bi-1*H*-imidazole, 1,3-dibenzoyl-2,3-dihydro-, monohydrochloride (8,9); (65276-00-8)

2-(1,3-Dibenzoylimidazolidin-2-yl) imidazole hydrochloride: Imidazolidine, 1,3-dibenzoyl-2-(1*H*-imidazol-2-yl)-, monohydrochloride (8,9), (65276-01-9)

INDIRECT ELECTROLYSIS: TETRAMETHYL 1,1,2,2-ETHANETETRACARBOXYLATE

(1,1,2,2-Ethanetetracarboxylic acid, tetramethyl ester)



Submitted by DONALD A. WHITE¹

Checked by CARL R. JOHNSON and ROBERT C. ELLIOTT

1. Procedure

The preparation is carried out in a 500-mL, three-necked flask equipped with two graphite rod electrodes (Note 1). To the flask are added 132 g (1.0 mol) of dimethyl 1,3-propanedioate (Note 2), 15 g (0.10 mol) of sodium iodide, and 300 mL of methanol. A thermometer and reflux condenser are attached; the mixture is stirred and the solution formed is heated to 60°C. The heat source is removed. The solution is electrolyzed with a constant current of 2.0 A (Note 3) for 13.5 hr (Note 4) with gentle magnetic stirring. After a few minutes of electrolysis, the electrolyte begins to reflux gently and reflux is maintained throughout the electrolysis period by the heating effect of current passage (Note 5). Small granular crystals of the product begin to separate toward the end of the electrolysis period.

After electrolysis the reaction mixture is allowed to cool to room temperature and is filtered (Note 6). The crystalline residue is washed three times with 100-mL portions of methanol, dried by suction on the filter, and finally dried under vacuum. The product (88.4–91 g, 67–69%) is obtained as a white solid, mp 134–135°C.

2. Notes

1. The electrodes are 12 × ¼ in. graphite rods such as those used by glassblowers in shaping softened glass. They are attached as shown (p. 3) via thermometer adaptors (Ace Glass Company, Vineland, NJ) and a specially made glass adaptor having two

10/18 and one 34/45 standard-taper joints. The electrodes should extend as far as possible into the electrolyte without interfering with the operation of the magnetic stirrer.

2. Dimethyl 1,3-propanedioate (dimethyl malonate) was obtained from Aldrich Chemical Company, Inc., and used as supplied.

3. A Heath/Schlumberger dc power supply, Model SP-2711, 30 V, 3 A, operating in its constant current mode, was used.

4. The current passed is 1.01 Faraday (1 Faraday = 26.8 A-hr) and this is sufficient to convert 75–80% of the starting material to product. At higher conversions further oxidation occurs, leading to formation of tetramethyl ethenetetracarboxylate and hexamethyl 1,1,2,2,3,3-propanehexacarboxylate. The latter has solubility properties similar to those of the desired product. The product may be contaminated with the propanehexacarboxylate ester if the reaction is taken to higher conversions.

5. The cell voltage was initially 15 V and rose to 18 V at the end of the electrolysis. The cell voltage should be in the range 15–20 V so that the heat generated can be controlled by reflux. Since the cell voltage changes only slightly during the course of the electrolysis, a constant-voltage power supply could be used.

6. The filtrate contains only 2–5 g of the desired product; recovery is not worthwhile. The filtrate can, however, be reused as the electrolyte for conversion of further propanedioate ester.

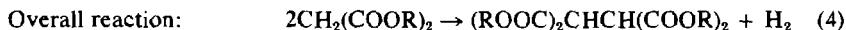
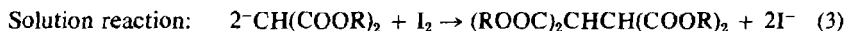
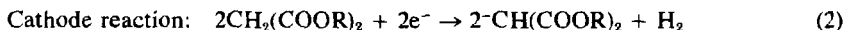
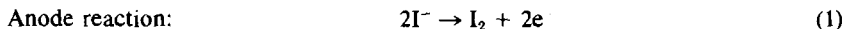
7. The product may be recrystallized (from methanol), which gives material with mp 135–136°C.

8. The product gave an acceptable C,H analysis; the molecular weight by osmometry in chloroform was found to be 258 ($C_{10}H_{14}O_8$ in theory 262). The product showed 1H NMR ($CDCl_3$) δ : 3.8, 4.2.

3. Discussion

The propanedioate (malonate) carbanion can be oxidized directly at an anode to give ethanetetracarboxylate esters, presumably via a radical intermediate.^{2–4} Competing oxidation of solvent leads to a mixture of products^{3,4} and for preparative purposes it is advantageous to carry out the reaction via indirect electrolysis as reported here. Indirect electrolysis refers to the continuous generation and regeneration of a reagent at an electrode, which inter-

acts with the substrate, as opposed to direct reaction of the substrate at the electrode. In the present case iodine is generated at the anode (1) and reacts with the cathodically generated (2) carbanion as shown (3) to give the desired overall reaction (4):



The present procedure is based on literature reports^{6,7} using indirect electrolysis involving electrogenerated halogens. Ethanetetra-carboxylate esters have also been prepared by the chemical reaction of propanedioate carbanions with halogens.⁸⁻¹⁰ The present procedure has the advantage of providing in situ generation of both the carbanion and the halogen from a small amount of added sodium halide. In other work it has been shown that the anodic formation of ethanetetra-carboxylate ester can be paired with cathodic conversion of propenoate (acrylate) to hexanedioate (adipate) esters.^{11,12} In addition to these routes based on propanedioate esters, ethanetetra-carboxylate esters have been obtained by electro-carboxylation of *cis*-butenedioate (maleate) esters.^{13,14}

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Appendix

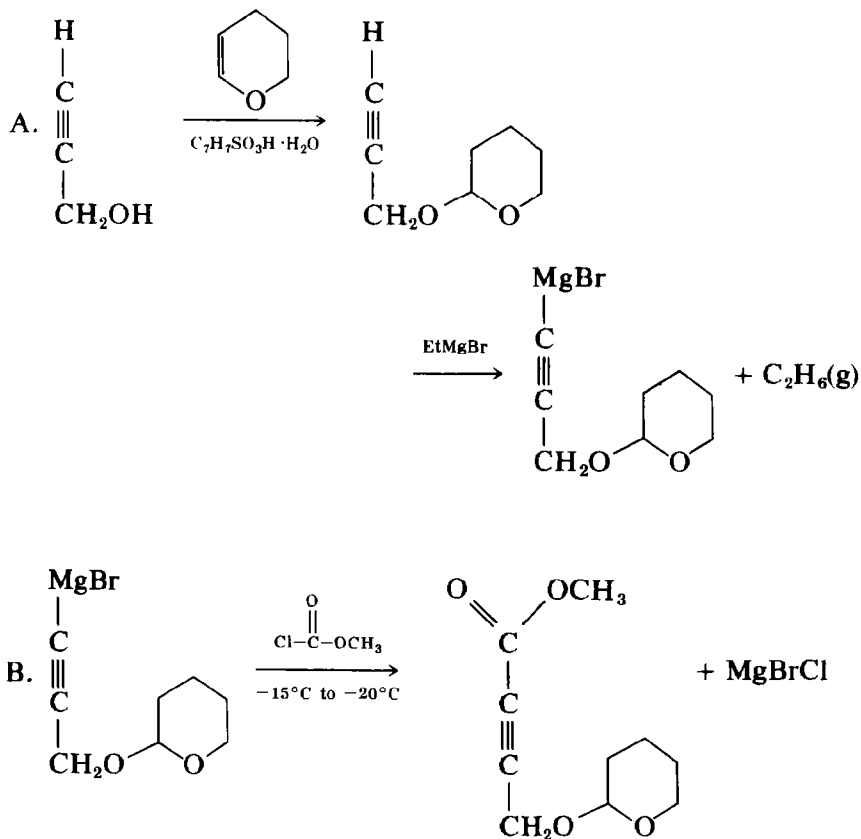
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

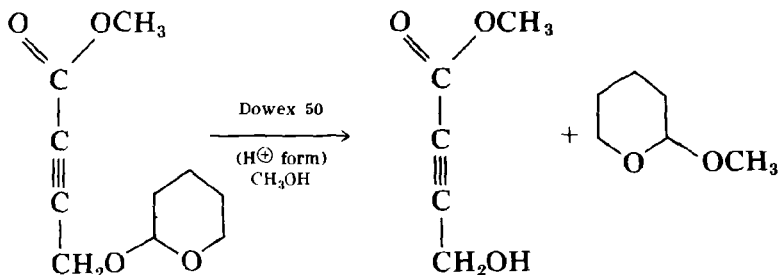
Tetramethyl 1,1,2,2-Ethanetetracarboxylate: 1,1,2,2-Ethanetetracarboxylic acid, tetramethyl ester (8,9); (5464-22-2)

Dimethyl 1,3-Propanedioate: Malonic acid, dimethyl ester (8); Propanedioic acid, dimethyl ester (9); (108-59-8)

METHYL 4-HYDROXY-2-BUTYNOATE

(2-Butynoic acid, 4-hydroxy-, methyl ester)





Submitted by R. A. EARL¹ and L. B. TOWNSEND²
 Checked by G. SAUCY and G. WEBER

1. Procedure

Caution! Acetylenic compounds are potentially explosive and methyl 4-hydroxy-2-butynoate is a potent vesicant (Note 1).

A. Tetrahydropyranyl derivative of propargyl alcohol [tetrahydro-2-(2-propynyloxy)-2H-pyran]. Two crystals (ca. 10 mg) of *p*-toluenesulfonic acid monohydrate are added to 268 g (291.3 mL, 3.2 mol) of warm (60°C) dihydropyran (Note 2) in a 1-L three-necked, round-bottomed flask equipped with a magnetic stirring bar, a thermometer, a dropping funnel containing 168 g (174.5 mL, 3.0 mol) of propargyl alcohol (Note 2) and a reflux condenser fitted with a drying tube. Stirring is started, and the propargyl alcohol is added (Note 3) as a thin stream during a period of ca. 30 min. The reaction is mildly exothermic, and the temperature is maintained at 60–65°C by controlling the rate of addition of the propargyl alcohol and by occasional external cooling with an ice bath. After the addition is completed, the temperature is monitored for another 30 min; slight cooling is sometimes necessary to keep the temperature in the range of 60–65°C. The reaction mixture is stirred for a total of 1.5 hr after the addition is completed, and then 0.5 g of powdered sodium bicarbonate is added and the mixture stirred for another hour. The mixture is then gravity-filtered into a 1-L, round-bottomed flask. The reaction mixture is distilled through a 45-cm Vigreux column under reduced pressure (Note 15). A small forerun (ca. 40 mL) with a bp of 45°C (15–20 mm) is followed by the product, bp 47–50°C (3.5–5 mm), 330–355 g (78–92%) (Note

15); $n_D^{22} = 1.4559$ (Note 16); ^1H NMR (90 MHz, neat) δ : 4.63 (s, 1, H_1), 4.03 (d, 2, $\text{C}\equiv\text{C}-\text{CH}_2-\text{O}$, $J = 2$ Hz), 3.17–3.84 (m, 2, $\text{H}_{5',5''}$), 2.47 (t, 1, $\text{C}\equiv\text{C}-\text{H}$, $J = 2$ Hz); 1.18–1.93 (br m, 6, $\text{H}_{2',2''}$, $\text{H}_{3',3''}$, $\text{H}_{4',4''}$); IR (neat) cm^{-1} : 3300 ($\text{C}\equiv\text{C}-\text{H}$), 2117 ($\text{C}\equiv\text{C}$ stretch).

B. Methyl 4-hydroxy-2-butyrate. One mole of ethylmagnesium bromide (Note 4) in diethyl ether is poured into a dry (Note 5) 2-L, three-necked, round-bottomed flask fitted with a mechanical stirrer and a glass stirrer bearing (Note 6), a dropping funnel fitted with a nitrogen-inlet tube, and an efficient condenser fitted with a drying tube. Stirring is started, and a solution of 140 g (1.0 mol, 141 mL) of the tetrahydropyranyl derivative of propargyl alcohol in 1-L of dry (Note 7) tetrahydrofuran is added during ca. 30 min (Note 8). Stirring is continued for an additional 1.5 hr, during which time a dry 3-L, three-necked flask is fitted with a mechanical stirrer, immersion thermometer, and dropping funnel. The 3-L flask is charged with a solution of 104 g (1.10 mol, 85.4 mL) of methyl chloroformate (Note 2) in 250 mL of tetrahydrofuran and the contents stirred and cooled to -20°C with a dry ice-acetone bath. Under gentle nitrogen pressure the acetylenic Grignard reagent is transferred portionwise through a $\frac{1}{4}$ -in. polypropylene tube to the dropping funnel attached to the 3-L, three-necked flask (Note 9). The acetylenic Grignard reagent is then added dropwise during 1.5 hr to the well-stirred solution of methyl chloroformate in tetrahydrofuran while the temperature is maintained at -15°C to -20°C by external cooling. After the addition is completed, the light brown reaction mixture is stirred another 30 min at -15°C , followed by another 1.5 hr at ice temperature. The reaction mixture is then stored without stirring for 12 hr at $+3^\circ\text{C}$, during which time the remaining magnesium salts separate from solution. The salts are removed by filtration (Note 10) and washed with three 150-mL portions of cold (0°C), dry toluene. The supernatant and washings are combined and concentrated (Note 11) to ca. 500-mL volume. The dark brown solution is then washed five times with 100-mL portions of saturated brine followed by drying over anhydrous sodium sulfate. The solution is concentrated to remove the toluene and then dissolved (Note 12) in 1 L of anhydrous methanol; 25 mL of Dowex 50-X4 cation resin (H^+ form, prewashed with anhydrous methanol) is then added and the

mixture stirred for 1.5 hr at 25°C. The ion-exchange resin is removed by filtration through a sintered-glass filter and is then washed with two 50-mL portions of anhydrous methanol. Solvent and 2-methoxytetrahydropyran are removed by concentration using a water aspirator and then an oil pump at 0.5-mm pressure. The residue from the concentration is then treated a second time (Note 13) with 1 L of anhydrous methanol and 25 mL of Dowex 50, followed by concentration as before. The residue is then distilled through a Claisen head to give methyl 4-hydroxy-2-butynoate (Note 14), 69–74 g (60–65%), bp 66–69°C/0.2 mm, $n_D^{22} = 1.4684$ (Note 17); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{SO}$) δ : 5.57 (t, 1, OH), 4.31 (d, 2, CH_2 , $J = 6$ Hz), 3.79 (s, 3, OCH_3); IR (neat) cm^{-1} : 3410 (OH), 2240 ($-\text{C}\equiv\text{C}-$), 1715 (ester).

2. Notes

1. Acetylenic compounds are potentially explosive, and all concentrations and distillations should be carried out behind a safety shield. Methyl 4-hydroxy-2-butynoate is a potent vesicant that causes painful burns on contact with skin. All operations should be carried out in an efficient fume hood and gloves should be worn at all times.

2. As supplied by Aldrich Chemical Company, Inc. (97% purity).

3. The general method of Robertson,³ whereby toluenesulfonic acid monohydrate is added to a mixture of an alcohol and dihydropyran, is not recommended for this preparation since the reaction is rather exothermic. Reaction temperatures below 60°C are to be avoided for the same reason since unreacted reagents accumulate and the reaction may suddenly get out of hand with resulting boiling and colorization of the reaction mixture.

4. Ethylmagnesium bromide was obtained from Aldrich Chemical Company, Inc. in the form of a 3 M solution in diethyl ether containing 133.3 g of ethylmagnesium bromide. Alternately, the ethylmagnesium bromide could be prepared by a standard procedure.⁴

5. Glassware was dried in an oven at 110°C, assembled while still hot, and flushed with dry nitrogen as the assembly cooled to room temperature. All reactions involving the Grignard reagents

were carried out under an atmosphere of dry nitrogen and in a fume hood.

6. The bearing was lubricated with mineral oil.

7. Anhydrous tetrahydrofuran from Matheson, Coleman and Bell Chemical Company was used for the reactions. Freshly opened bottles gave no effervescence when mixed with powdered calcium hydride. If smaller amounts of tetrahydrofuran are used, the acetylenic Grignard reagent often crystallizes out of the reaction mixture.

8. Vigorous gas evolution (highly flammable ethane gas) and boiling take place during the addition.

9. This type of transfer technique⁵ is preferred to open-air transfer to minimize losses due to hydrolysis by atmospheric moisture.

10. Filtration and subsequent washing of the hygroscopic salts are best carried out by replacing the dropping funnel in the reaction vessel with a sintered-glass filter stick. The reaction mixture is kept under a slightly positive nitrogen pressure while the supernatant is led from the filter stick through a polypropylene tube to a suction flask that is kept under a slightly negative pressure with the help of an aspirator.

11. Concentrations were carried out using a rotary evaporator and at a pressure of 12–15 mm and a temperature not exceeding 35°C unless otherwise noted.

12. The crude product at this stage shows the following ¹H NMR (CDCl₃) δ: 4.81 (bs, 1, H₁'), 4.36 (s, 2, C≡C—CH₂), 3.76 (s, 3, OCH₃), 3.26–4.08 (m, 2, H₅',₅'), 1.22–1.97 (m, 6 H, H₂',₂', H₃',₃', H₄',₄').

13. Distillation of the residue after the first treatment with Dowex 50 and methanol gives a product containing 7–10% of the tetrahydropyranyl derivative of methyl 4-hydroxy-2-butyrate. Removal of the by-product 2-methoxytetrahydropyran and retreatment with Dowex 50 and methanol give a product containing only 0.5–1.5% of the unblocked alcohol.

14. The distillate often turns a light pink or yellow color in the receiver flask.

15. The checkers found that distillation at a pressure of 15–20 mm (submitters) gave a somewhat lower yield (78–84%). A slight

yield improvement (78–94%) was obtained by the checkers by using lower pressure in the distillation.

16. The submitters reported n_D^{22} 1.4595.

17. The submitters reported n_D^{22} 1.4720.

3. Discussion

The preparation of the tetrahydropyranyl derivative of propargyl alcohol is a modification of a published³ general procedure that is simple and useful for large-scale preparations.

Methyl 4-hydroxy-2-butynoate has been prepared⁶ in 83% yield by treatment of 4-hydroxy-2-butynoic acid with 2% sulfuric acid in methanol and in 65% yield by carboxylation in an autoclave of the Grignard reagent of 1-(tetrahydropyran-2'-yloxy)prop-2-yne followed by treatment with 10% sulfuric acid in methanol. 4-Hydroxy-2-butynoic acid has been prepared⁶ in 65% yield by treating the Grignard reagent of propargyl alcohol with carbon dioxide in an autoclave for 24 hr followed by acidic hydrolysis with aqueous 10% sulfuric acid. 4-Hydroxy-2-butynoic acid has also been prepared⁷ in an unspecified yield by bubbling carbon dioxide for 14 days through a suspension of the Grignard derivative of propargyl alcohol in ether.

The first part of the procedure illustrates a method for the preparation of the tetrahydropyranyl derivative of an alcohol which requires no extraction or wash procedures during the workup of the product.

The second part of the preparation illustrates a very efficient, mild method for the preparation of a highly reactive α,β -acetylenic ester via the carbomethoxylation of the Grignard reagent of a terminal acetylenic compound with methyl chloroformate. This preparation of methyl 4-hydroxy-2-butynoate obviates the necessity⁶ of carrying out the carboxylation of an acetylenic Grignard reagent in an autoclave. This procedure also eliminates the necessity⁶ of carrying out the continuous ether extraction of 4-hydroxy-2-butynoic acid from an aqueous phase.

The use of a mixture of a strongly acidic cation-exchange resin and methanol to remove a tetrahydropyranyl protecting group offers a very mild method of deblocking that does not require the use of a base during the workup.

Methyl 4-hydroxy-2-butyne-1-carboxylate has been used⁶ as a starting material for the preparation of an δ -hydroxy- α,β -acetylenic ester. It has also been employed⁸ as a dipolarophile in a 1,3-dipolar cycloaddition reaction that resulted in the first synthesis of 8-aza-3-deazaguanosine.

1. Hercules, Inc., Baccchus Works, Magna, UT 84064
2. Department of Medicinal Chemistry, College of Pharmacy, University of Michigan, Ann Arbor MI 48109
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl 4-hydroxy-2-butyne-1-carboxylate: 2-Butynoic acid, 4-hydroxy-, methyl ester (8,9); (31555-05-2)

2H-Pyran, tetrahydro-2-(2-propynyloxy)- (8,9); (6089-04-9)

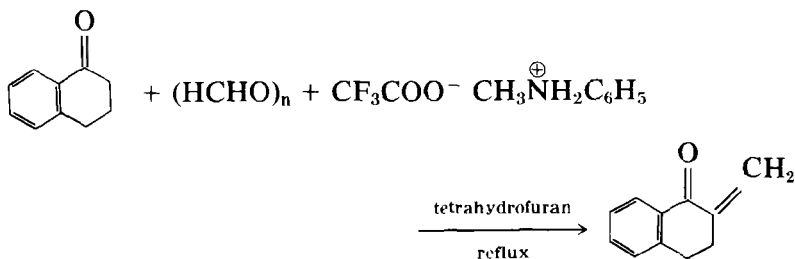
Dihydropyran: 2H-Pyran, 3,4-dihydro- (8,9); (110-87-2)

Propargyl alcohol: 2-Propyn-1-ol (8,9); (107-19-7)

Methyl chloroformate: Formic acid, chloro-, methyl ester (8); Carbonochloridic acid, Methyl ester (9); (79-22-1)

**METHYLENE KETONES AND ALDEHYDES BY
SIMPLE, DIRECT METHYLENE TRANSFER: 2-METHYLENE-
1-OXO-1,2,3,4-TETRAHYDRONAPHTHALENE**

(1(2*H*)-Naphthalenone, 3,4-dihydro-2-methylene-)



Submitted by JEAN-LOUIS GRAS¹

Checked by KERRY J. GOMBATZ and GEORGE BÜCHI

1. Procedure

A 250-mL flask equipped with a reflux condenser is charged with 6.75 g (0.225 mol) of paraformaldehyde (Note 1) and 16.57 g (0.075 mol) of *N*-methylanilinium trifluoroacetate (Note 2). A solution of 7.30 g (0.05 mol) of α -tetralone (Note 3) in 50 mL of dry tetrahydrofuran (Note 4) is added at room temperature. The *N*-methylanilinium trifluoroacetate dissolves, and the magnetically stirred mixture is refluxed for 4 hr under a nitrogen atmosphere (Note 5). During this time a red color develops and the paraformaldehyde dissolves after 2 hr. After 4 hr the heating oil bath is removed and the red solution allowed to cool for 10 min. Diethyl ether (100 mL) is gradually added under efficient magnetic stirring, which induces the separation of a red gum. The ethereal solution is decanted from the red gum into a separatory funnel and washed with 50 mL of half-saturated sodium bicarbonate solution. The red gum is triturated with 50 mL of diethyl ether, and the resulting ethereal solution is then used to extract the washing water (Note 6). The combined organic layers are dried over magnesium sulfate. Filtra-

tion and concentration of the extract, first on a rotary evaporator then under high vacuum, afford 8.05–8.6 g of a heavy red oil (Note 7). Trituration of this oil with 70 mL of diethyl ether precipitates impurities and causes some polymerization. Filtration through Celite and concentration under high vacuum give 6.8–7.2 g (86–91%) of material that solidifies in a freezer (Note 8). Further purification by column chromatography over silica gel affords analytically pure material (mp 46–46.5°C) but lowers the yield to 70–82%.

2. Notes

1. Paraformaldehyde is sometimes sold commercially under the label "polyoxymethylene," and commercial polyoxymethylene (Prolabo—France) was used.

2. This crystalline white salt can be obtained by adding dropwise 1 mol of commercial trifluoroacetic acid (Fluka AG) to a stirred solution of 1 mol of commercial *N*-methylaniline (Fluka AG) in 1 L of dry diethyl ether in a nitrogen atmosphere with cooling in an ice bath. After addition the solution is stirred magnetically for 1 hr. The white precipitate that forms is filtered, washed with 100 mL of pentane, and dried overnight in a desiccator under high vacuum. The salt (195 g, 88%) thus obtained had mp 66.5°C.

3. Commercial α -tetralone, 95% pure, was purchased from Fluka AG and used without purification.

4. Tetrahydrofuran was distilled from the ketyl prepared from benzophenone and sodium, but the reaction does not suffer from moisture. Dioxane can also be used, but the iminium salt polymerizes rapidly at the reflux temperature of this solvent (101°C). To avoid polymerization the *N*-methylanilinium trifluoroacetate should be added in portions to the reaction mixture.

5. The reaction can be monitored by TLC. The α -methylene ketones exhibit higher *R_f* values than starting material when eluted in a diethyl ether–pentane (1:1) solvent system.

6. Workup and isolation should be completed in minimum time to avoid polymerization of the product. The heavy red gum thus obtained is soluble in methylene chloride and contains some β -methylene- α -tetralone.

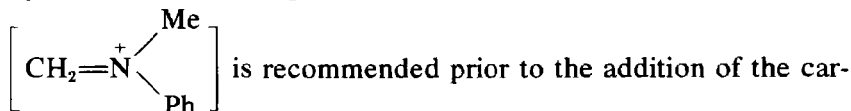
7. A TLC analysis reveals a major component accompanied by two minor, more polar impurities. Because of the relative insta-

bility of α -methylene carbonyl compounds, isolation of these substances is associated with dimerization or polymerization. This crude material exhibits satisfactory NMR and IR data and can be used as such for many synthetic purposes.

8. The checkers found that storage of this material at room temperature results in the total conversion to polymer in less than 12 hr. The stability of the product is greatly increased if it is stored at temperatures below -5°C . The spectral properties are as follows: IR (CCl_4) cm^{-1} 3065, 3030, 1680, 1620, 1604, 918; ^1H NMR (CCl_4) δ : 2.9 (singlet, 4), 5.37 (thin multiplet, 1), 6.17 (thin multiplet, 1), 7.3 (multiplet, 3), 8.07 (multiplet, 1).

3. Discussion

The procedure described herein demonstrates a general synthetic method to form α -methylene ketones by direct methylene transfer. A number of methods have been previously described and reviewed.^{2,3} The advantages of direct methylene transfer for the formation of α -methylene ketones are the aprotic, nearly neutral conditions utilized. Although the reaction is not regiospecific, it is highly sensitive to steric hindrance, and transfer occurs at the less hindered site of unsymmetrical ketones. The reaction has been applied to cyclic and acyclic ketones⁴ and extended to the synthesis of vinyl ketones⁵ and α -methylenealdehydes. It is not applicable to γ - or δ -lactones, or strained cyclic ketones such as norcamphor or cyclobutanone. With cyclohexanone, cyclopentanone, or aldehydes as substrates, pre-formation of the iminium intermediate



This can be achieved by heating the reagents to reflux in tetrahydrofuran for 20 min, followed by the addition of the carbonyl compound at reflux temperature or lower, if necessary. When higher reflux temperatures are required, dioxane can be used as a solvent. Addition in portions of *N*-methylanilinium trifluoroacetate to the reaction mixture minimizes polymerization of the iminium intermediate.

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5. Gras, J L *Tetrahedron Lett* **1978**, 2955-2958

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

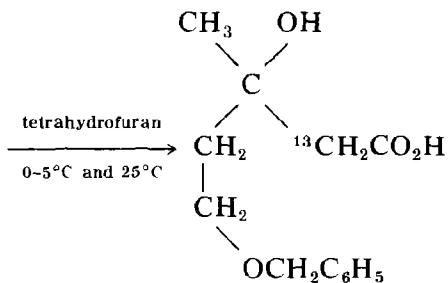
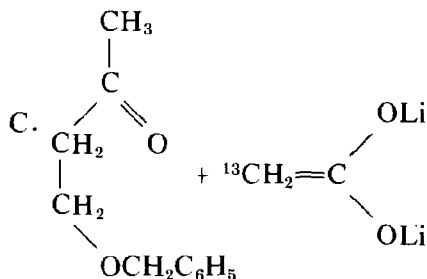
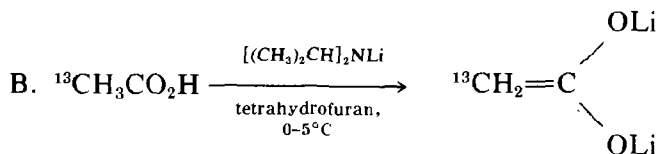
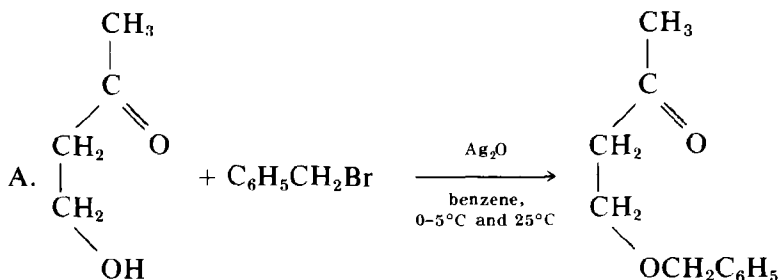
2-Methylene-1-oxo-1,2,3,4-tetrahydro-naphthalene: 1(2*H*)-Naphthalenone, 3,4-dihydro-2-methylene- (8,9); (13203-73-1)

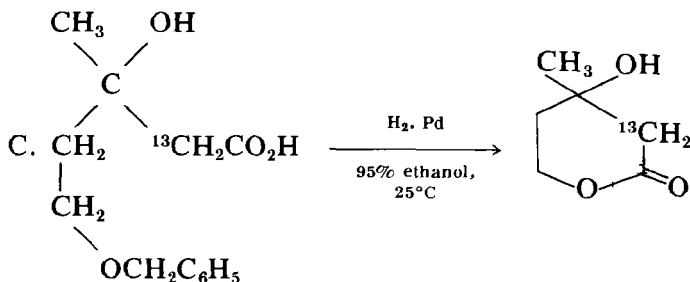
N-Methylanilinium trifluoroacetate: Aniline, *N*-methyl-, trifluoroacetate (8); Benzenamine, *N*-methyl-, trifluoroacetate (9); (29885-95-8)

α -Tetralone: 1(2*H*)-Naphthalenone, 3,4-dihydro- (8,9); (529-34-0)

(*R,S*)-MEVALONOLACTONE-2-¹³C

(2*H*-Pyran-2-one-¹³C, tetrahydro-4-hydroxy-4-methyl-)





Submitted by MASATO TANABE and RICHARD H. PETERS¹
 Checked by PAULA M. ROACH, SUNG W. RHEE,
 and ROBERT M. COATES

1. Procedure

Caution! Benzyl bromide is a lacrimator. This procedure should be conducted in a ventilated hood.

A. 4-Benzoyloxy-2-butanone. A 100-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a condenser mounted with a nitrogen inlet, and a pressure-equalizing dropping funnel (Note 1). The flask is charged with 4.40 g (0.050 mol) of 4-hydroxy-2-butanone (Note 2), 50 mL of dry toluene (Note 3), and 13.9 g (0.060 mol) of freshly prepared silver oxide (Note 4). The suspension is stirred and cooled in an ice bath while 12.0 g (0.070 mol) of benzyl bromide (Note 5) is added over ca. 5 min. The ice bath is removed, and the mixture is allowed to stir for 18 hr at room temperature (Note 6). The suspension is filtered through Celite, the filter cake is washed with two 50-mL portions of toluene, and the combined filtrates are evaporated under reduced pressure. The remaining liquid, which weighs 9.6–10.4 g, is dissolved in 15 mL of 5% tetrahydrofuran in hexane. The cloudy solution is applied to a 5 × 47.5 cm column prepared with 380–385 g of silica gel (Note 7) packed in 5% tetrahydrofuran in hexane. The column is eluted with 5% tetrahydrofuran in hexane, and 250-mL fractions are collected and analyzed by TLC (Note 8). A total of 12 or 13 fractions (3–3.25 L) is collected first to separate benzyl bromide, dibenzyl ether, and other minor by-products. The product is then eluted with 0.5–1.0 L of tetrahydrofuran, the solvent is evaporated, and the remaining 6.0–6.5 g of liquid is distilled under

reduced pressure. After separation of a 0.7–1.0 g forerun, bp 30–68°C (0.2 mm), consisting mainly of benzyl alcohol, 3.87–4.33 g (43–49%) of 4-benzyloxy-2-butanone, bp 77–79°C (0.2 mm), n_D^{25} 1.5018, is collected (Note 9).

B. 5-Benzyloxy-3-hydroxy-3-methylpentanoic-2- ^{13}C acid. A 50-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, a condenser connected to a nitrogen inlet, and a pressure-equalizing dropping funnel. The apparatus is purged with nitrogen and dried (Note 1), and the flask is charged with 1.79 g (2.4 mL, 0.0177 mol) of freshly distilled diisopropylamine and 6.5 mL of dry tetrahydrofuran (Note 10). The solution is stirred and cooled in an ice bath while 7.22 mL (0.0169 mol) of 2.34 *M* butyllithium in hexane (Note 11) is added from the dropping funnel over 30 min. After 30 min a solution of 0.439 g (0.00720 mol) of acetic acid-2- ^{13}C (Note 12) in 3 mL of tetrahydrofuran is added by syringe over ca. 10 min. The solution is stirred and cooled in an ice bath for 3.5 hr, after which 1.30 g (0.0073 mol) of 4-benzyloxy-2-butanone in 4 mL of tetrahydrofuran is added by syringe over 15 min. Stirring is continued for 2 hr at 0°C and 18 hr at room temperature. The reaction mixture is cooled in an ice bath, hydrolyzed by adding 4.5 mL of water, and concentrated under reduced pressure to remove most of the tetrahydrofuran. The remaining aqueous suspension is basified by addition of 6 mL of aqueous 4% sodium hydroxide and extracted with 30 mL of diethyl ether. The ethereal layer is extracted with 40 mL of 4% sodium hydroxide, the combined alkaline extracts are cooled and acidified to pH 3 with ca. 10 mL of 18% hydrochloric acid, and the aqueous mixture is extracted with three 25-mL portions of ether. The combined ethereal extracts are dried over anhydrous sodium sulfate and evaporated. The remaining viscous, yellow liquid weighs 0.95–1.01 g (55–59%) and is used in part C without further purification (Note 13).

C. Mevalonolactone-2- ^{13}C . In a 250-mL Paar hydrogenation bottle are placed 50 mL of 95% ethanol, 0.107 g (0.001 mol) of palladium black (Note 14), and 0.519 g (0.00217 mol) of 5-benzyloxy-3-hydroxy-3-methylpentanoic acid-2- ^{13}C . The bottle is attached to a Paar hydrogenation apparatus (Note 15), charged to 50 psig with hydrogen, and shaken at room temperature for 2 hr. The

hydrogen is flushed from the bottle with nitrogen, and the suspension is filtered by gravity through a layer of Celite with a medium-porosity sintered-glass Büchner funnel to separate the catalyst. *Caution! The palladium is pyrophoric and must always be kept wet with ethanol during filtration to prevent contact with air* (Note 16). The bed of Celite and adhering catalyst is rinsed with three 5-mL portions of ethanol. The combined filtrates are returned to the Paar bottle, 0.107 g (0.001 mol) of fresh palladium black is added, and the hydrogenation is continued for another 8 hr. The catalyst is separated by filtration as previously described, and the combined filtrates are evaporated under reduced pressure. Distillation of the residual liquid with a Kügelrohr apparatus at 90–100°C and 0.01 mm affords 0.235–0.249 g (83–88%) of mevalonolactone-2-¹³C as a slightly yellow oil (Note 17).

2. Notes

1. The apparatus was dried in an oven at 125°C and allowed to cool while a stream of nitrogen was passed through the condenser and out the dropping funnel. Alternatively the apparatus may be flushed with nitrogen and flamed dry. A nitrogen atmosphere was maintained within the apparatus during the subsequent operations.

2. 4-Hydroxy-2-butanone was purchased from Chemical Samples Company by the checkers and distilled, bp 56–58°C (5.0 mm). The submitters obtained the material from BASF Wyandotte Corporation, Parsippany, NJ 07054.

3. Toluene was dried over sodium wire for 36 hr.

4. The silver oxide was prepared by the following procedure. A solution of 6.9 g (0.172 mol) of sodium hydroxide in 200 mL of water was heated to 80–90°C and added to a solution of 30 g (0.177 mol) of silver nitrate in 200 mL of water, also heated to 80–90°C. The resulting hot suspension was quickly filtered, and the filter cake was washed with 200 mL of hot water, 200 mL of 95% ethanol, and 200 mL of absolute ethanol. The silver oxide was dried at 1 mm and weighed 17.8–18.3 g (87–89%).

5. Benzyl bromide was distilled before use, bp 89°C (14 mm).

6. The reaction is mildly exothermic, and the mixture becomes warm after the ice bath is removed. The checkers monitored the

progress of the reaction by TLC on silica gel with 5% methanol in chloroform as developing solvent. After 2 hr the spot at R_f 0.42 for the starting alcohol had disappeared, and the formation of the spots at R_f 0.70 and 0.47 for the product and benzyl alcohol, respectively, appeared to be complete.

7. The checkers used silica gel 60 having particle sizes from 0.05 to 0.2 mm (70-270 mesh ASTM), supplied by Brinkmann Instruments, Inc., Westbury, NY. The submitters used 450 g of silica gel with 90-200 mesh purchased from Gallard-Schlesinger Chemical Manufacturing Corp., Carle Place, NY 11514.

8. Thin-layer chromatograms were performed by the checkers on plates coated with silica gel using chloroform as developing solvent. The R_f values for benzyl bromide, dibenzyl ether, 4-benzyloxy-2-butanone, and benzyl alcohol were 0.72, 0.61, 0.20, and 0.09, respectively. Chromatograms of the crude product showed spots for these four components and in addition three minor spots at R_f 0.44, 0.40, and 0.36. The first six fractions (1.5 L) were combined and evaporated, affording 0.6–1.5 g of material judged to be mainly benzyl bromide. The following six or seven fractions (1.5–1.75 L) provided 1.6–3.2 g of material composed largely of dibenzyl ether.

9. The submitters obtained 4.5 g (51%) of product, bp 95°C (0.8 mm), n_D^{27} 1.5029. A boiling point of 88–91°C (0.5 mm) and a refractive index of n_D^{28} 1.5040 are reported for 4-benzyloxy-2-butanone.² The product was analyzed by the checkers. Analysis calculated for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.87; H, 8.09. The product has the following spectral characteristics: IR (liquid film) cm^{-1} : 1725 and 1710 (split C=O), 1360, 1175, 1110, 1090, 740, 700; 1H NMR ($CDCl_3$) δ : 2.17 (singlet, 3, CH_3), 2.70 (triplet, 2, $J = 6$, CH_2CH_2O), 3.78 (triplet, 2, $J = 6$, CH_2CH_2O), 4.50 (singlet, 2, $CH_2C_6H_5$), 7.32 (singlet, 5, C_6H_5).

10. Diisopropylamine was dried over potassium hydroxide pellets and distilled from barium oxide before use. The submitters purified tetrahydrofuran by distillation from lithium aluminum hydride. For a warning concerning the potential hazards of this procedure, see *Org. Synth.*, Coll. Vol. 5, 1976, 976. The checkers distilled the solvent from the sodium ketyl of benzophenone.

11. Butyllithium in hexane is available from Alfa Products, Ventron Corporation. The submitters standardized the butyllithium

solution by titration of diphenylacetic acid in tetrahydrofuran.³ The concentration of the butyllithium solution was determined by the checkers by titration of a 1-mL aliquot in 10 mL of benzene with 1 *M* 2-butanol in xylene using 1,10-phenanthroline as indicator.⁴

12. Acetic acid-2-¹³C of 90% isotopic purity was purchased by the checkers from Stohler Isotope Chemicals, Rutherford, NJ, and dried by distillation from phosphorus pentoxide in the following manner. A 0.5-g portion of the labeled acetic acid was transferred to a 5-mL flask containing 0.1 g of phosphorus pentoxide. The flask (A) was attached to a vacuum system (see Figure 1), chilled with a dry ice-acetone bath until the mixture solidified, and evacuated to 0.01 mm. The stopcock was closed, the cooling bath was moved to the receiver (flask B), and flask A was allowed to warm to room temperature. The distillation was completed by heating flask A to 60°C. Nitrogen was introduced into the system and flask B removed and stoppered. The recovery of acetic acid-2-¹³C was 0.42–0.44 g (84–86%).

13. The submitters carried out the procedure in part B at five times the scale described with 1.96 g (0.0321 mol) of acetic acid-2-¹³C and obtained 4.01 g (56%) of product. The spectral properties of the product are as follows: IR (liquid film) cm^{-1} : 1710 (C=O); ¹H NMR (CDCl₃) δ : 1.31 (doublet, ca. 2.4, *J* = 4.5, ¹³CH₂CCH₃),

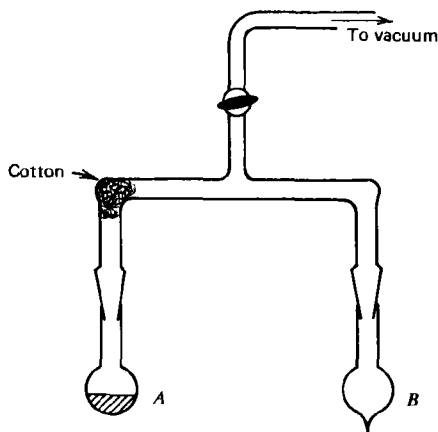


Figure 1

1.31 (singlet, ca. 0.6, $^{12}\text{CH}_2\text{CCH}_3$), 1.89 (multiplet, 2, $\text{CH}_2\text{CH}_2\text{O}$), 2.55 (doublet, ca. 1.6, $J = 128$, $^{13}\text{CH}_2\text{CO}_2\text{H}$), 2.55 (singlet, ca. 0.4, $^{12}\text{CH}_2\text{CO}_2\text{H}$), 3.70 (triplet, 2, $J = 6$, $\text{CH}_2\text{CH}_2\text{O}$), 4.52 (singlet, 2, $\text{C}_6\text{H}_5\text{CH}_2$), 7.35 (singlet, 5, C_6H_5). The product may be purified further by Kugelrohr distillation with an oven temperature of 100–110°C (0.015 mm).

14. The palladium black was purchased from Engelhard Industries Division, Engelhard Minerals and Chemicals Corporation, Iselin, NJ 08830. The checkers found that the hydrogenolysis may also be effected with 5% palladium on carbon, although 20 hr was required to achieve complete reaction.

15. The hydrogenation apparatus is available from Paar Instrument Company, Inc., Moline, IL 61265.

16. As a further precaution the checkers chilled the suspension in an ice bath prior to filtration.

17. The product was further purified by the checkers by recrystallization from ca. 1.5 mL of ether at 0°C. The recovery of white, crystalline mevalonolactone-2- ^{13}C , mp 24–26°C, was 90–92%. The reported² melting point is 27–28°C. The spectral properties of the product are as follows: IR (liquid film) cm^{-1} : 3300 (OH), 1730 ($\text{C}=\text{O}$); 220-MHz ^1H NMR (CDCl_3) δ : 1.40 (doublet, ca. 2.4, $J = 4.5$, $^{13}\text{CH}_2\text{CCH}_3$), 1.40 (singlet, ca. 0.6, $^{12}\text{CH}_2\text{CCH}_3$), 1.90 (multiplet, 2, $\text{CH}_2\text{CH}_2\text{O}$), 2.54 and 2.67 (eight-line ABX multiplet, ca. 1.6, $J_{AB} = 17$, $J_{AX} = 132$, $J_{BX} = 127$, $^{13}\text{CH}_A\text{H}_B$), 2.54 and 2.67 (AB doublet, 0.4, $J = 17$, $^{12}\text{CH}_A\text{H}_B$), 4.47 (multiplet, 2, $\text{CH}_2\text{CH}_2\text{O}$).

3. Discussion

The important role of mevalonate in the biosynthesis of terpenes and sterols has been the impetus for the development of numerous syntheses of the parent mevalonolactone^{5–9} and a host of labeled analogs.^{7–9} Mevalonolactone has been prepared by reduction of dimethyl or diethyl 3-hydroxy-3-methylglutarate in two stages with lithium aluminum hydride and hydrogen¹⁰ or sodium borohydride¹¹; by reduction of monomethyl 3-hydroxy-3-methylglutarate with lithium borohydride^{12,13} or sodium in liquid ammonia¹³; by reduction of mevaldic acid or its esters with borohydride,^{11a,14,15} hydrogen,^{14b} or NADPH in enzyme preparations¹⁶; by reduction of *N*-(diphenylmethyl)-3,4-epoxy-5-hydroxy-3-methylpentanamide with lithium borohydride followed by hydrolysis¹⁷; by oxidation of

3,5-dihydroxy-3-methylpentanal and its derivatives with hydrogen peroxide in acetic acid¹⁸ or formic acid,⁸ or with aqueous bromine¹⁹; by oxidation of 3-methyl-1,3,5-pentanetriol with chromium trioxide^{20a} or silver carbonate^{20b}; by ozonolysis of 3-methyl-1-tetrahydropyranyloxy-5-hexen-3-ol^{6,21}; by hydrolysis of 3,5-dihydroxy-3-methylpentanenitrile²²; by degradation of linalool²³; and by Reformatsky reactions of acetate with a variety of 4-substituted 2-butanones.

The Reformatsky reactions of methyl or ethyl bromoacetate with 4-acetoxy-,^{2,24} 4-benzyloxy-,² 4-tetrahydropyranyloxy-,² 4-chloro-,⁶ and 4,4-dimethoxy-2-butanone^{14,18} have been carried out. The adducts were converted to mevalonolactone by hydrolysis and, in the case of the acetal reactant, by appropriate reduction and oxidation procedures. The same Reformatsky-type syntheses of mevalonolactone have also been performed using the lithium and magnesium carbanions of acetate esters^{5,19,25,26} and the dianion of acetic acid^{26,27} instead of the usual zinc reagent. The intramolecular Reformatsky reaction of 4-(bromoacetoxy)-2-butanone gives mevalonolactone directly.²⁸ A related route to mevalonolactone involves boron trifluoride-catalyzed cycloaddition of ketene to 4-acetoxy-2-butanone followed by hydrolysis.^{18a}

Many of the procedures given above have been utilized for the preparation of mevalonolactone labeled with isotopes of carbon, hydrogen, and oxygen.⁷⁻⁹ Mevalonolactone-¹⁴C has been prepared with the label at all six positions: 1-,^{7,29} 2-,^{7,14a,24} 3-,^{11b} 3',^{20a,30} 4-,^{7,18a} and 5-¹⁴C.¹⁹ Preparations of singly and doubly labeled mevalonolactone-¹³C have been reported recently: 2-,^{26,31} 3-,³² 4-,³³ 3',⁴⁻,^{7,18a} 3,4-,^{26,33b} and 4,5-¹³C.³⁴ The procedure described here²⁶ for the preparation of mevalonolactone-2-¹³C is both convenient and economical compared to the usual Reformatsky methods since acetic acid-2-¹³C is utilized directly in the condensation reaction, rather than methyl or ethyl bromoacetate. The overall yield of mevalonolactone-2-¹³C is 46–52% based on acetic acid-2-¹³C.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(*R,S*)-Mevalonolactone-2-¹³C: 2*H*-Pyran-2-one-3-¹³C, tetrahydro-4-hydroxy-4-methyl- (8,9); (53771-22-5)

2-Butanone, 4-benzyloxy- (8); 2-Butanone, 4-phenylmethoxy- (9); (6278-91-7)

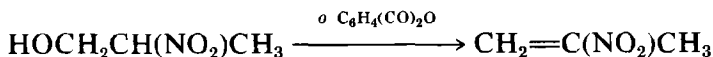
2-Butanone, 4-hydroxy- (8,9); (590-90-9)

5-Benzyloxy-3-hydroxy-3-methylpentanoic-2-¹³C acid; Valeric-2-¹³C acid, 5-benzyloxy-3-hydroxy-3-methyl- (8); Pentanoic-2-¹³C acid, 3-hydroxy-3-methyl-5-(phenylmethoxy)- (9); (57830-65-6)

Acetic-2-¹³C acid (8,9), (1563-80-0)

2-NITROPROPENE

(1-Propene, 2-nitro)



Submitted by MASAOKI MIYASHITA, TETSUJI YANAMI,
and AKIRA YOSHIKOSHI¹

Checked by D SEEBACH, H SIEGEL, and E WILKA

1. Procedure

Caution! This procedure should be carried out in a hood since 2-nitropropene is a powerful lacrimator. Nitroolefins have a tendency to undergo “fume-offs” (which can be like explosions) near the end of a distillation, particularly if air is let in on a hot distillation residue (from a vacuum distillation).

A 250 mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar is charged with 96.5 g (0.65 mol) of phthalic

anhydride (Note 1) and 52.5 g (0.50 mol) of 2-nitro-1-propanol (Note 2). A 10-cm vacuum-insulated Vigreux column, a stillhead fitted with a thermometer, a condenser, a 50-mL, round-bottomed receiving flask, and a water aspirator are installed in due order, and the reaction vessel is placed in an oil bath and evacuated to 110 mm (Note 3). The bath temperature is raised to 150°C and maintained for 30 min while the phthalic anhydride melts to give a homogeneous solution. The receiving flask is immersed in an ice bath, stirring is started, and the bath temperature is raised to 180°C. As the reaction mixture darkens, green-colored 2-nitropropene is gradually distilled off with water, bp 50–65°C (110 mm). The bath temperature is held at 180–185°C until the distillation ceases (ca. 1 hr). The distillate is transferred into a 50-mL separatory funnel, and the lower layer is separated from water (Note 4) and dried over anhydrous magnesium sulfate. Redistillation under reduced pressure through a 10-cm vacuum-insulated Vigreux column (Note 5) gives 25.0–31.4 g (57–72%) of 2-nitropropene, which is collected in an ice-cooled receiving flask as a transparent green liquid, bp 56–57°C (86 mm), n_D^{20} 1.4348 [lit.³ bp 58°C (90 mm), n_D^{19} 1.4292, d_4^{20} 1.0492] (Note 5).

2. Notes

1. Commercial phthalic anhydride, purchased from Wako Pure Chemical Industries, Ltd. (Japan) or from Fluka AG, Buchs (Switzerland), was used without purification.

2. The checkers purchased 2-nitro-1-propanol (ca. 98% purity) from EGA-Aldrich and used it without further purification. The submitters prepared this reagent from nitroethane and formalin according to the procedure of Feuer,² yield 70–75%, bp 79–80°C (5 mm).

3. Lower pressure may cause a loss of the product because of its volatility.

4. The layers sometimes do not separate well. In this case a small amount of magnesium sulfate should be added.

5. It is important that the bath temperature be kept as low as possible to avoid fume-off decompositions. In the checked procedure the bath temperature was never allowed to exceed 80°C. Toward the end of the distillation the pressure was reduced to ca.

60 mm to achieve complete distillation. Although pure 2-nitropropene may be stored in a freezer as a low-melting solid for several weeks, it is recommended to prepare it immediately before use since it tends to polymerize and to darken slowly on storage. 2-Nitropropene polymerizes readily in the presence of a trace of alkali.

3. Discussion

The procedure described is essentially the same as that of Buckley and Scaife.³ The yield has been increased from 55.5% up to 72% by using 1.3 mol eq of phthalic anhydride and by carefully controlling the pressure and cooling the receiving flask. Although 2-nitropropene has previously been prepared by pyrolysis of 2-nitro-1-propyl benzoate in 72% overall yield from 2-nitro-1-propanol,⁴ the present method is preferred for its preparation since the procedure is much simpler and the product is directly obtainable from 2-nitro-1-propanol without first preparing its ester. It is also applicable to the preparation of 1-nitro-1-propene (58%),^{5,6} 2-nitro-1-butene (82%),⁷ and 2-nitro-2-butene (60%).^{6,7} In general, aliphatic nitroolefins have the tendency to polymerize readily with alkali.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

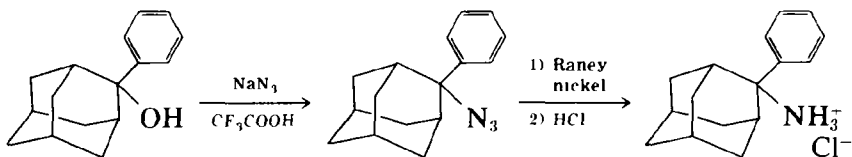
1-Propene, 2-nitro- (8,9); (4749-28-4)

Phthalic anhydride (8); 1,3-Isobenzofurandione (9); (85-44-9)

1-Propanol, 2-nitro- (8,9); (2902-96-7)

2-PHENYL-2-ADAMANTANAMINE HYDROCHLORIDE

(Tricyclo[3.3.1.1^{3,7}]decan-2-amine, 2-phenyl, hydrochloride)



Submitted by ASHER KALIR and DAVID BALDERMAN¹

Checked by CARL R. JOHNSON and DEBRA L. MONTICCIOLO

1. Procedure

Caution! The reaction should be carried out in a good hood.

A. 2-Azido-2-phenyladamantane. A 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, a pressure-equalizing dropping funnel, and a thermometer is charged with 125 mL of chloroform and 13 g (0.2 mol) of sodium azide. The mixture is cooled with an ice-salt bath to -5°C to 0°C , and 37.5 mL (0.5 mol) of trifluoroacetic acid is added, followed after 5–10 min with 22.8 g (0.1 mol) of 2-phenyl-2-adamantan-2-ol (Note 1). The resulting slurry is stirred for 4 hr at 0°C and then allowed to reach room temperature overnight. The mixture is cautiously neutralized with a slight excess of 12–15% aqueous ammonia solution and transferred to a separatory funnel. The chloroform layer is separated, and the aqueous solution is extracted with 50 mL of chloroform. The combined organic extracts are washed with 50 mL of water, separated, and dried over magnesium sulfate. The solvent is removed in a rotary evaporator. The oily residue solidifies on cooling. The yield is 23.6–24.8 g (93–98%), mp $42\text{--}45^\circ\text{C}$. Recrystallization of a sample from 2-propanol raises the melting point to $47\text{--}48^\circ\text{C}$ (Note 2).

B. 2-Phenyl-2-adamantanamine hydrochloride. A solution of 24 g (0.095 mol) of the crude 2-azido-2-phenyladamantanane in 75 mL of 2-propanol is placed in a 1-L beaker fitted with a mechanical stirrer, and heated in a water bath that can be removed quickly.

Wet, active Raney nickel (Notes 3 and 4) is added in portions at 60–70°C with stirring until the evolution of nitrogen ceases (Note 5). The mixture is heated for an additional 10 min, filtered through a Büchner funnel, and washed with 75 mL of 2-propanol in such a manner that the catalyst is always covered with liquid (Note 6). The filtrate is concentrated in a rotary evaporator under reduced pressure. The crude residue is dissolved in 75 mL of toluene and treated with 22 mL of concentrated hydrochloric acid while stirring. The 2-phenyl-2-adamantanamine hydrochloride is collected, triturated with 50 mL of warm acetone, filtered again, and air-dried. The yield is 22.5–24.0 g (90–96%), and the product melts at 293–296°C (closed capillary) (Notes 7 and 8).

2. Notes

1. 2-Phenyl-2-adamantanol² is prepared by adding 25 g (0.167 mol) of 2-adamantanone (Note 3) in several portions to phenylmagnesium bromide, obtained from 40 g of bromobenzene and 6.5 g of magnesium turnings in 200 mL of diethyl ether. The solution is stirred for 1 hr and worked up with aqueous ammonium chloride. The organic layer is separated, dried over magnesium sulfate, concentrated, and the oily residue is crystallized from petroleum ether. The yield is 25.5 g (67%) of crystals melting at 77–78°C. The crude oily residue may be used in the next step without purification.

2. The product is characterized by IR (CCl₄) cm^{-1} : 2075; ¹H NMR (CCl₄) δ : 1.72 and 2.40 (s, 14 H), 7.20 (s, 5 H).

3. 2-Adamantanone was obtained from Aldrich Chemical Company, Inc. Active Raney nickel catalyst was obtained from W. R. Grace Company.

4. The amount of Raney nickel depends on its hydrogen content. Usually 25–35 g is sufficient.

5. A large vessel is required because of excessive frothing. The frothing may be controlled by adding a little cold 2-propanol, by removing the heating, or by stopping the stirrer.

6. *Caution! Dry catalyst is pyrophoric.*

7. The free 2-phenyl-2-adamantanamine may be liberated from the salt by adding a solution of ammonia or sodium hydroxide, extracting with toluene, concentrating, and distilling under reduced

pressure; bp 120–122°C (0.15 mm); n_D^{17} 1.5850; ^1H NMR (CCl_4) δ : 1.30 (s, 2H, NH_2), 1.68 and 2.26 (br s, 14 H, adamantane protons), 7.1 (m, 5H, Ph).

8. Similarly 2-butyl-2-adamantanamine hydrochloride, mp 300–305°C, is obtained from 2-butyl-2-adamantanol³ in 30% yield.

3. Discussion

The present procedure is an example of preparation of tertiary phenylcarbinylamines, and is in many cases superior to methods based on the Ritter reaction,⁴ and Hofmann⁵ or Curtius degradation.⁶ The availability of starting materials, fair yields of products, and the simplicity of operations (there is no need to isolate any intermediates or to use a hydrogenation apparatus) are the main advantages of this procedure. The azide synthesis is adapted from procedures described for the preparation of 1,1-diphenyl-2-azidoethane⁷ and 1-phenyl-1-azidocyclohexane.⁸ The azides are quite stable and could be distilled under reduced pressure. The amines and their substitution products are physiologically active agents.^{4,9}

A number of compounds have been prepared by this method (the isolation of hydrochloride can be omitted), as listed in Table I.¹⁰

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

2-Adamantanamine, 2-phenyl-, hydrochloride (8); Tricyclo [3.3.1.1^{3,7}]decan-2-amine, 2-phenyl-, hydrochloride (9); (–)

TABLE I
AMINES FROM TERTIARY ALCOHOLS

Alcohol	Azide ^a	Amine		
	Bp (°C) (mm Hg)	Bp (°C) (mm Hg)	Yield (%)	Starting Material
2-Phenyl-2-propyl	106 (22)	100 (22)	66	α -Methylstyrene
1-Phenylcyclopentyl	139–140 (38)	128–130 (20)	40	Cyclopentanone
1-Phenylcyclohexyl		115–120 (5)	38	Cyclohexanone
2-Methyl-1-phenylcyclohexyl	90–91 (0.25)	150–153 (23)	66	2-Methyl-1-phenylcyclohexanol
1-Phenylcycloheptyl	153–155 (23)	163–165 (25)	45	Cycloheptanone
2-Phenyl-2-norbornyl	150–155 (25)	163–165 (28)	51	2-Norbornanone

^aThe azides contain up to 15–20% of the corresponding phenylalkenes.

Adamantane, 2-azido-2-phenyl- (8); Tricyclo[3.3.1.1^{3,7}]decane, 2-azido-2-phenyl- (9); (65218-96-4)

2-Adamantanol, 2-phenyl- (8); Tricyclo[3.3.1.1^{3,7}]decan-2-ol, 2-phenyl- (9); (29480-18-0)

2-Adamantanone (8); Tricyclo[3.3.1.1^{3,7}]decanone (9); (700-58-3)

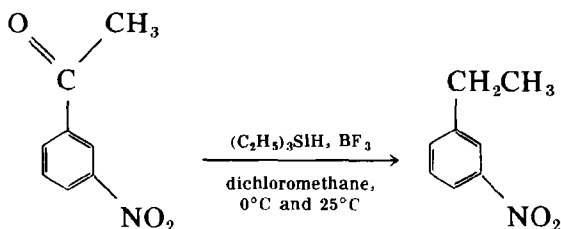
2-Adamantanamine, 2-phenyl- (8); Tricyclo[3.3.1.1^{3,7}]decan-2-amine, 2-phenyl- (9); (—)

2-Adamantanamine, 2-butyl-, hydrochloride (8); Tricyclo[3.3.1.1^{3,7}]decan-2-amine, 2-butyl-, hydrochloride (9); (—)

2-Adamantanol, 2-butyl- (8); Tricyclo[3.3.1.1^{3,7}]decan-2-ol, 2-butyl- (9); (14451-86-6)

REDUCTION OF KETONES TO HYDROCARBONS WITH TRIETHYLSILANE: *m*-NITROETHYL BENZENE

(Benzene, 1-ethyl-3-nitro-)



Submitted by JAMES L. FRY, STEVEN B. SILVERMAN,
and MICHAEL ORFANOPOULOS¹

Checked by JACK W. MUSKOPF and ROBERT M. COATES

1. Procedure

Caution! Boron trifluoride gas is highly corrosive; this preparation should be conducted in a well-ventilated hood.

A dry, 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a gas-inlet tube (Note 1), a pressure-equalizing dropping funnel, and a Dewar condenser cooled with ice-water and fitted with a drying tube containing anhydrous calcium sulfate (Drierite). A solution of 20.9 g (0.180 mol) of tri-

ethylsilane (Note 2) in 80 mL of dichloromethane (Note 3) is placed in the flask. The solution is stirred rapidly and cooled in an ice bath while boron trifluoride gas (Note 4) is introduced below the surface of the liquid at a moderate rate. The first appearance of white fumes at the exit of the drying tube (Note 5) indicates that the solution is saturated and the apparatus is filled with boron trifluoride. The flow of boron trifluoride is adjusted to a level sufficient to maintain a slight emission of white fumes from the drying tube, and a solution of 10.0 g (0.0606 mol) of *m*-nitroacetophenone (Note 6) in 30 mL of dichloromethane is added dropwise during 10 min. Stirring and cooling are continued for 30 min, after which the flow of boron trifluoride gas is stopped and the cooling bath is removed. The mixture is stirred at room temperature for 20 min, cooled again with the ice bath, and hydrolyzed by adding 20 mL of aqueous saturated sodium chloride. The upper organic layer is decanted from the salts, which are then dissolved in 50 mL of water. The aqueous solution is extracted with two 25-mL portions of pentane, which are combined with the original organic layer. The organic solution is washed with two 25-mL portions of saturated sodium chloride and dried with anhydrous sodium sulfate. Distillation at atmospheric pressure through a 10-cm Vigreux column serves to separate solvent and ca. 15 g of a mixture of primarily triethylsilane and triethylfluorosilane, bp 106–109°C (Note 7). The remaining liquid is distilled in a short-path distillation apparatus under reduced pressure, affording 8.33–8.38 g (91–92%) of pale yellow *m*-nitroethylbenzene, bp 120–121°C (15 mm), 134–135°C (22 mm), n_D^{25} 1.5330 (Note 8).

2. Notes

1. A Pasteur pipet clamped in an O-ring thermometer adapter served as a convenient, adjustable gas-inlet tube. The large end of the pipet was fitted with a small rubber septum, through which a syringe needle was passed for introducing the boron trifluoride gas.

2. Triethylsilane was purchased from either Petrach Systems, Inc., P.O. Box 141, Levittown, PA 19059, or PCR Research Chemicals, Inc. P.O. Box 1778, Gainesville, FL 32602. The reagent was dried with anhydrous sodium sulfate and distilled before use, bp 107–108°C.

3. Reagent-grade dichloromethane was extracted repeatedly with concentrated sulfuric acid, washed twice with water, dried with anhydrous calcium chloride, and distilled from phosphorus pentoxide before use.²

4. A cylinder of boron trifluoride gas was purchased from Linde Division, Union Carbide Chemical Corporation. The gas was passed through Teflon tubing to a 250-mL gas-washing bottle equipped with a fritted-glass inlet and containing a saturated solution of boric anhydride (ca. 16 g) in 150 mL of concentrated sulfuric acid. Another section of Teflon tubing was connected to the exit port of the gas-washing bottle and to the barrel of a 2-mL, gas-tight syringe which fitted into the syringe needle in the septum. Boric anhydride (boron oxide) is available from Fisher Scientific Company. The purpose of the boric anhydride-sulfuric acid scrubber is to remove hydrogen fluoride.³ All ground-glass joints in the system were lined with Nalgene or Teflon standard-taper sleeves to prevent them from sticking together. Nalgene standard-taper sleeves are supplied by Nalge Sylron Corporation, Rochester, NY 14602. Any stopcocks used should be Teflon. The checkers placed one empty 250-mL trap in the gas line before the gas-washing bottle and another after it.

5. The submitters recommend that the effluent gases be directed toward a water trap to reduce the amount of boron trifluoride and hydrogen fluoride released into the atmosphere.

6. *m*-Nitroacetophenone was supplied by Aldrich Chemical Company, Inc., and recrystallized from ethanol, mp 76–78°C. The compound may also be prepared by the method of Corson and Hazen.⁴

7. If desired, the mixture of triethylsilane and triethylfluorosilane can be reconverted into triethylsilane by reduction with lithium aluminum hydride.⁵

8. The product was analyzed by the checkers. Analysis calculated for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.51; H, 6.17; N, 9.04. The spectral properties of the product are as follows: IR (CCl_4) cm^{-1} : 3100, 3075, 2975, 2940, 2880, 1532, 1348, 1095, 895; 1H NMR ($CDCl_3$) δ : 1.27 (triplet, 3, $J = 7.5$, CH_3), 2.74 (quartet, 2, $J = 7.5$, CH_2), 7.3–8.1 (multiplet, 4, aromatic H); ^{13}C NMR ($CDCl_3$) δ : 14.7, 28.2, 120.4, 122.2, 128.8, 133.9, 145.9, 148.2.

3. Discussion

This procedure illustrates a method for the selective reduction of a carbonyl group to a methylene group in compounds having other potentially reducible functional groups. The method is applicable to the reduction of aryl aldehydes without electron-withdrawing ring substituents, aryl alkyl ketones, diaryl ketones, and dialkyl ketones.⁶ Under the above conditions, aryl aldehydes having strongly electron-withdrawing ring substituents (viz. NO_2 , CN) and alkyl aldehydes yield alcohols. Benzylic alcohols and secondary or tertiary aliphatic alcohols are also reduced to hydrocarbons under these reaction conditions,⁷ as are some epoxides.⁸ Functional groups that are not affected during ketone reductions include nitro, cyano, ether, ester, carboxylate, and ring halogens.

The effectiveness of this reduction procedure is related to the ability of free boron trifluoride to coordinate strongly to the carbonyl oxygen and to the strong driving force provided by the formation of the silicon-fluorine bond.⁶ Similar carbonyl reductions using organosilicon hydrides in conjunction with Brønsted acids^{9,10} or boron trifluoride etherate¹¹ are generally only successful with aryl ketones and aldehydes bearing electron-donating ring substituents; with other carbonyl substrates by-products other than hydrocarbons become the predominant products.

Other carbonyl reduction methods include the familiar Clemmensen¹² and Wolff-Kishner¹³ reactions. These are usually conducted for extended periods of time at elevated temperatures under strongly acidic or basic conditions, respectively. Mixed metal hydride-Lewis acid reagents constitute strong reducing systems that are often effective in the deoxygenation of diaryl ketones and some aryl alkyl ketones. However, even the mixed lithium aluminum hydride-aluminum chloride¹⁴ and sodium borohydride-boron trifluoride¹⁵ reagents reduce dialkyl ketones only to the corresponding alcohols, often with the formation of significant amounts of olefinic by-products. *m*-Nitroethylbenzene has been prepared by reductive deamination of 4-amino-3-nitroethylbenzene¹⁶ and by nitration of ethylbenzene and subsequent fractional distillation to separate the isomers.¹⁷

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17. For example, see Brown, H C , Bonner, W H *J Am Chem Soc* **1974**, 76, 605-606

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

m-Nitroethylbenzene: Benzene, 1-ethyl-3-nitro- (8,9); (7369-50-8)

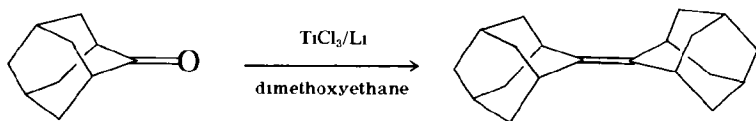
Silane, triethyl- (8,9); (617-86-7)

m-Nitroacetophenone: Acetophenone, 3'-nitro- (8); Ethanone, 1-(3-nitrophenyl)- (9); (121-89-1)

Silane, triethylfluoro- (8,9); (358-43-0)

REDUCTIVE COUPLING OF CARBONYLS TO ALKENES: ADAMANTYLIDENEADAMANTANE

(Tricyclo[3.3.1.1^{3,7}]decane, tricyclo[3.3.1.1^{3,7}]decylidene-)



Submitted by MICHAEL P. FLEMING and JOHN E. MCMURRY¹
Checked by STEVEN R. VILLASEÑOR and CARL R. JOHNSON

1. Procedure

A 2-L, three-necked flask is thoroughly flamed while being flushed with argon and is then fitted with three rubber septa. Anhydrous titanium trichloride (63.16 g, 0.409 mol) (Notes 1 and 2) is added to the weighed flask in an argon-filled glove bag. The flask is reweighed, and one of the rubber septa is replaced with a dry (12 h at 120°C) reflux condenser through which a stream of argon is flowing (Note 3). The flask is fitted with a mechanical stirrer equipped with a glass shaft and Teflon paddle (Note 4). Into the flask is syringed 600 mL of 1,2-dimethoxyethane (Note 5), and the remaining rubber septum is exchanged for a glass stopper. Lithium (8.52 g, 1.23 mol) (Note 6) is etched to brilliance in methanol, quickly washed in petroleum ether (Note 7), and cut into small pieces directly into the stirred suspension. The mixture is heated at reflux for 1 hr by an oil bath that is then removed (Note 8). Immediately after the solvent has ceased to reflux, 2-adamantanone (15.36 g, 0.102 mol) (Note 1) is added in one portion, and the mixture is heated at reflux for 18 hr.

Stirring is maintained as the mixture is allowed to cool to room temperature, and 600 mL of petroleum ether (Note 7) is added in 100-mL portions at 5-min intervals (Note 9). The stirrer is disconnected from its motor, and the solution is poured into a sintered-glass funnel containing 50 g of Florisil (approximately 7 cm in

depth) (Note 1). The black material remaining in the reaction vessel is washed with eight 50-mL portions of petroleum ether which are poured into the same pad of Florisil (Notes 10 and 11). The filter pad is then washed with 400 mL of petroleum ether. Removal of the solvent from the combined filtrates by means of a rotary evaporator followed by high vacuum (0.05 mm) gives 12–13 g of a white crystalline solid. This crude product is dissolved in 3.5 L of hot methanol (Note 1), and the volume is reduced to 2 L by boiling. The solution is allowed to slowly cool to room temperature. The colorless needles are vacuum filtered through sintered glass (medium frit) and washed with 50 mL of ice-cold methanol. The crystals are dried under vacuum (0.05 mm Hg) to give 10.3–10.4 g (75–76%) of adamantylideneadamantane, mp 184–186°C; ^1H NMR (CDCl_3) δ : 1.5–2.1 (br m, 24 H) 2.7–3.1 (br m, 4 H). Concentration of the mother liquor to 350 mL and crystallization as described above yields an additional 1.2–1.5 g (9–11%) of product, mp 182–184°C (Note 12).

2. Notes

1. The following reagents were used as supplied: titanium trichloride from Alfa Products, Ventron Corporation; 2-adamantanone from Aldrich Chemical Company, Inc.; methanol from Matheson, Coleman and Bell; and acetone from Mallinckrodt, Inc.

2. Because of its sensitivity toward oxygen and water, anhydrous titanium trichloride should always be handled under an inert atmosphere. The submitters report that titanium trichloride in bottles that have been opened and resealed undergoes a slow deterioration that causes erratic results in the coupling reaction. This decomposition is frequently detectable by the evolution of white fumes from the titanium trichloride during transfer. If a number of small-scale reactions are to be performed, the use of a Schlenk tube is advisable to extend the useful life of the titanium trichloride.

3. Substitution of nitrogen for argon does not significantly decrease the yield.

4. The coupling reaction may be adversely affected if metallic stirrers are employed. The bore of the stirrer should be water

cooled. Lubricants such as mineral oil are to be avoided since they complicate product isolation.

5. The 1,2-dimethoxyethane was obtained from Aldrich Chemical Company, Inc., and was allowed to stand over molecular sieves (type 4A in $\frac{1}{16}$ -in. pellet form from Union Carbide Corporation) for several days. Final purification was accomplished by heating at reflux over potassium in a nitrogen atmosphere for at least 10 hr, followed by distillation from potassium. The solvent was used on the same day that it was distilled to minimize the formation of peroxides.

6. Lithium wire (3.2-mm diam, 0.02% sodium) was obtained from Alfa Products, Ventron Corporation, and was washed in petroleum ether before weighing.

7. Petroleum ether (bp 35–65°C) was obtained from Fisher Scientific Company and was distilled from potassium permanganate.

8. The color of the reaction mixture at this point varies from gray-green to gray-black. The success of the reaction seems to be independent of the color.

9. Addition of petroleum ether causes a viscous black precipitate to cling to the walls of the flask, leaving a milky-white solution that can be conveniently poured into the filter.

10. The black residue, which consists of inorganic salts, titanium, and unreacted lithium, is retained in the reaction vessel, where it is washed with petroleum ether while the mass is manually stirred with the paddle. No problem has been encountered in exposing the black material to the air during the washing procedure.

11. The black residue is destroyed in the following manner. The stirrer motor is reattached, and the flask is flushed with argon. The flask is cooled in an ice-water bath before adding 300 mL of petroleum ether and 300 mL of acetone. As the mixture is vigorously stirred, ca. 10 mL of methanol is added from a dropping funnel. *After reaction has begun* (an induction period of up to 0.5 hr may occur before gas evolution becomes noticeable), an additional 590 mL of methanol is added dropwise over a 6–10 hr period. Stirring is continued at 0°C until pieces of lithium can no longer be seen (approximately 1 hr after the addition of the methanol has been completed).

12. The second crop is slightly impure, as shown by its NMR spectrum.

3. Discussion

Adamantylideneadamantane has been prepared by (1) photolysis of 2-adamantylketene dimer,² (2) reduction of 4*e*-chloroadamantylideneadamantane with sodium in liquid ammonia,³ (3) rearrangement of spiro[adamantane-2,4'-homoadamantan-5'-ol] with Lewis acids,^{4,5} (4) reduction of 2,2-dibromoadamantane with magnesium⁶ or zinc-copper couple,⁷ and (5) treatment of the azine of 2-adamantanone with hydrogen sulfide, followed by oxidation with lead tetraacetate and heating with triphenylphosphine.⁸

The present method is a modification of a previous procedure by the submitters.⁹ Handling of lithium in the air is less hazardous and more convenient than that of potassium, which was originally used. The higher-boiling solvent 1,2-dimethoxyethane was found to produce higher yields than when tetrahydrofuran was employed. Although the titanium trichloride-lithium system results in slightly lower yields for aliphatic ketones than the corresponding potassium method, the former is considerably more convenient for large-scale reactions. The lithium procedure is applicable to both aromatic and aliphatic aldehydes and ketones (Table I). Reductive coupling of unsymmetrical carbonyl compounds usually results in a mixture of geometric isomers.

TABLE I
REACTION OF KETONES AND ALDEHYDES WITH TITANIUM
TRICHLORIDE-LITHIUM IN 1,2-DIMETHOXYETHANE

Carbonyl Compound	Yield of Alkene Product (%)
Acetophenone	94
Benzaldehyde	97
Benzophenone	96
Cholestanone	84
Cyclododecanone	90
Cycloheptanone	85
Cyclohexanone	81
Decanal	59
Hexanal	58 (28 : 72, <i>cis</i> : <i>trans</i>)

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

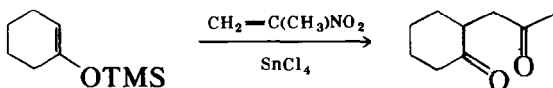
Adamantylideneadamantane: $\Delta^{2,2'}$ -Biadamantane (8); Tricyclo[3.3.1.1^{3,7}]decane, tricyclo[3.3.1.1^{3,7}]decylidene- (9); (30541-56-1)

Titanium trichloride: Titanium chloride (TiCl₃) (8,9); (7705-07-9)

2-Adamantanone (8); Tricyclo[3.3.1.1^{3,7}]decanone (9); (700-58-3)

SYNTHESIS OF 1,4-DIKETONES FROM SILYL ENOL ETHERS AND NITROOLEFINS: 2-(2-OXOPROPYL)CYCLOHEXANONE

(Cyclohexanone, 2-(2-oxopropyl))



Submitted by MASAOKI MIYASHITA, TETSUJI YANAMI,
and AKIRA YOSHIKOSHI¹

Checked by DONALD HILVERT, STEFAN KWIATKOWSKI,
and DIETER SEEBACH

1. Procedure

Caution! This preparation should be carried out in a hood since 2-nitropropene is a powerful lacrimator and anhydrous stannic chloride is a skin irritant.

A 1-L, three necked, round-bottomed flask is fitted with a magnetic stirring bar and a pressure-equalizing dropping funnel to which is attached an oil bubbler, a rubber septum, and an argon or nitrogen inlet to maintain a static inert gas atmosphere in the reaction vessel throughout the reaction. The flask and dropping funnel are charged with 500 mL of dry methylene chloride and 40 mL (34 g, 0.20 mol) of 1-trimethylsilyloxy-1-cyclohexene (Note 1), respectively. The flask is flushed with dry inert gas and immersed in a cooling bath at ca. -78°C (acetone or 2-propanol-dry ice). Stirring is started and 23 mL (52.1 g, 0.20 mol) of anhydrous stannic chloride (Note 2) is added rapidly through the rubber septum by means of a syringe. Then 20.0 mL (21.0 g, 0.23 mol) of 2-nitropropene (Note 3) is added through the rubber septum by a syringe over a period of 5–10 min, giving a green solution. The reaction mixture is further stirred at -78°C for 20 min, and then the silyl enol ether is added dropwise to the mixture over 1 hr, giving a faint yellow solution. After completion of the addition the resulting solution is stirred at ca. -78°C for an additional hour, then the bath temperature is gradually warmed to -5°C over a period of 3–3.5 hr while the stirring is continued (Note 4). The inert gas flow is stopped, the dropping funnel is replaced by a condenser, the magnetic stirrer is removed, and the flask is equipped with a heating mantel and an overhead stirring device. Then 280 mL of water are added, and the resulting heterogeneous mixture is vigorously stirred at reflux for 2 hr (Note 5). The mixture is subsequently cooled to room temperature and then poured into a 1-L separatory funnel and the methylene chloride layer is separated from the water. The aqueous layer is extracted once with 100 mL of methylene chloride, and the combined organic layers are washed twice with 160-mL portions of cold water (Note 6) and once with saturated brine, dried over anhydrous magnesium sulfate, and filtered. The solvent is removed on a rotary evaporator and the residual oil is distilled through a 10-cm Vigreux column under reduced pressure to yield 18.7–21.5 g (61–70%) of 2-(2-oxopropyl)cyclohexanone as a fragrant yellow liquid, bp $84\text{--}85^{\circ}\text{C}$ (0.8 mm), $n_{\text{D}}^{19} 1.4671$ [lit⁵ bp $91\text{--}93^{\circ}\text{C}$ (1.1 mm), $n_{\text{D}}^{25} 1.4655$] (Note 7).

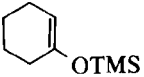
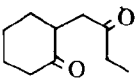
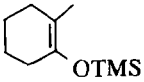
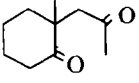
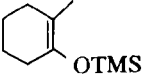
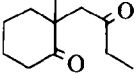
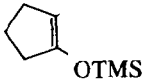
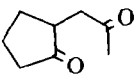
2. Notes

1. This silyl enol ether was prepared according to the procedure of House,^{2a} 80%, bp 75°C (21 mm) [lit^{2a} 74–75°C (20 mm)].
2. A fresh bottle of commercial anhydrous stannic chloride purchased from Wako Pure Chemical Industries, Ltd., Japan, or from Fluka AG, Buchs, Switzerland, was used without purification.
3. 2-Nitropropene³ was freshly prepared before use.
4. The yellow solution becomes green on warming and finally turns yellow.
5. On addition of water the mixture turns purple, and after refluxing it becomes brown.
6. Although an insoluble white substance appears in the aqueous washings, it is discarded.
7. The checkers found refractive indices n_D^{19} 1.4668 and 1.4665 or n_D^{25} 1.4657 and 1.4649.

3. Discussion

This procedure illustrates a recently published, simple, general method for the synthesis of 1,4-diketones from silyl enol ethers and nitroolefins.⁴ 2-(2-Oxopropyl)cyclohexanone has been prepared by the reaction of the pyrrolidine enamine of cyclohexanone with bromoacetone (40%)⁵ and by several other multistep processes.^{6–8} However, the overall yields obtained by these routes have never exceeded 50% and some of the methods are laborious for large-scale preparations. The present method illustrates a mild and convenient one-pot reaction for the preparation of 1,4-diketones. In addition, the starting materials are readily accessible, the reaction proceeds regioselectively, and the yields of product are generally high. This process consists of the initial Michael addition of silyl enol ethers to nitroolefins, followed by a Nef reaction of the nitronate esters.⁴ The scope of the reaction is shown in Table I. The 1,4-diketones thus obtained have been converted into corresponding cyclopentenones in high yields.⁴

TABLE I
1,4-DIKETONES PREPARED FROM SILYL ENOL ETHERS AND NITROOLEFINS

Silyl Enol Ether	Nitroolefin	Lewis Acid	1,4-Diketone	Yield (%)
	2-Nitro-1-butene	TiCl ₄		76
	2-Nitropropene	TiCl ₄		70
	2-Nitro-1-butene	TiCl ₄		82
	2-Nitropropene	SnCl ₄		70

1. Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai 980, Japan.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

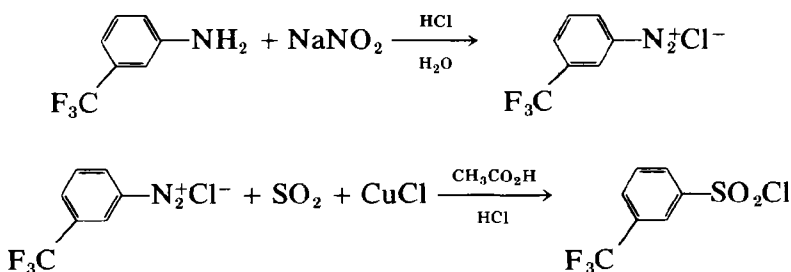
Cyclohexanone, 2-acetyl- (8); Cyclohexanone, 2-(2-oxopropyl)- (9); (6126-53-0)

1-Trimethylsilyloxy-1-cyclohexene: Silane, (1-cyclohexen-1-yloxy)trimethyl- (8,9); (6651-36-1)

1-Propene, 2-nitro- (8,9); (4749-28-4)

***m*-TRIFLUOROMETHYLBENZENESULFONYL CHLORIDE**

(Benzenesulfonyl chloride, *m*-(trifluoromethyl)-)



Submitted by R. V. HOFFMAN¹

Checked by G. SAUCY, G. P. ROTH, and J. W. SCOTT

1. Procedure

Caution: All operations should be carried out in a hood! m-Trifluoromethylbenzenesulfonyl chloride is a lacrimator. Spills should be treated with saturated sodium carbonate.

α,α,α -Trifluoro-*m*-toluidine (*m*-aminobenzotrifluoride) (96.7 g, 0.6 mol) (Note 1) is added in one portion to a mixture of concentrated hydrochloric acid (200 mL) and glacial acetic acid (60 mL) in a 1000-mL beaker arranged for efficient mechanical stirring (Note 2). The white hydrochloride salt precipitates (Note 3). The beaker is placed in a dry ice-ethanol bath and, when the temperature of the stirred mixture has reached -10°C , a solution of sodium nitrite (44.8 g, 0.65 mol) in water (65 mL) is added dropwise at such a rate that the temperature does not exceed -5°C (Note 4). After all the sodium nitrite solution has been added, the mixture is stirred for 45 min while the temperature is maintained between -10°C and -5°C (Note 5).

While the diazotization is being completed, glacial acetic acid (600 mL) is placed in a 4000-mL beaker and stirred magnetically. Sulfur dioxide is introduced by a bubbler tube with a fritted end immersed below the surface of the acetic acid until saturation is evident (Note 6). Cuprous chloride (15 g) (Note 7) is added to the

solution. The introduction of sulfur dioxide is continued until the yellow-green suspension becomes blue-green. Most of the solids dissolve during this time (20–30 min). The mixture is then placed in an ice bath and cooled with stirring. When the temperature approaches 10°C, the diazotization reaction mixture (Note 8) is added in portions over a 30-min period to the sulfur dioxide solution. Considerable foaming occurs after each addition, and this can be disrupted with a few drops of ether. The temperature rises during the addition, but it should not exceed 30°C. After all the diazonium salt mixture has been added, the mixture is stirred without cooling for 30 min. The green reaction mixture is poured into ice water (1 : 1, 2000 mL), stirred magnetically until the ice has melted, and added to a 4000-mL separatory funnel. The product separates as a yellow oil which is drawn off. The reaction mixture is extracted with 200-mL portions of ether until the ether washings are colorless (Note 9), and these washings are added to the initial product. The combined organic fraction is washed with saturated aqueous sodium bicarbonate until neutral (Note 10), then with water, and is then dried with magnesium sulfate. The solvent is removed with a rotary evaporator, and the residue is distilled (bp 54–55°C, 0.1 mm) through a 10-cm vacuum-jacketed Vigreux column to give *m*-trifluoromethylbenzenesulfonyl chloride (100–115 g, 68–79%) as a colorless or slightly yellow, clear liquid (Note 11, 12).

2. Notes

1. α,α,α -Trifluoro-*m*-toluidine was obtained from Aldrich Chemical Company, Inc. The checkers distilled this material prior to use (bp 187–189°C).

2. A chain beaker clamp is very satisfactory for supporting the beaker, as it can later be used as a handle to pour the diazonium solution. For efficient stirring the blade of the stirrer was made by trimming the ends of a large Teflon stirring paddle to the diameter of the beaker. The paddle was inverted (straight edge on bottom) and should rotate 1–1.5 cm from the bottom of the beaker.

3. If solid amines are used, they should be thoroughly crushed in a mortar and pestle before adding to the acid mixture.

4. Temperature control during the sodium nitrite addition is essential to the success of the preparation. The temperature can go as low as -15°C but must not exceed -5°C . The addition takes ca. 1 hr. At temperatures greater than -5°C , dark red by-products form which lower the yield.

5. Temperature control is conveniently accomplished by raising and lowering the dry-ice bath. It does not seem to matter if longer reaction times are employed, but the temperature should be lowered to -10°C or below after 45 min.

6. Saturation, which requires 15–30 min, is conveniently noted by observing that most sulfur dioxide bubbles reach the surface of the acetic acid.

7. The original literature² suggests that copper(II) chloride dihydrate can be used as a catalyst, since it is reduced by the sulfur dioxide to copper(I). It has been noted on several occasions that catalytically inactive mixtures result. If copper(II) chloride dihydrate is used, it is expedient to add copper(I) chloride (1g) to ensure efficient catalysis in the early stages of the reaction.

8. This mixture should be a pale tan suspension, and it should be cooled between additions.

9. The first portion of ether may be larger (400 mL) since much is dissolved into the aqueous mixture. A total of 1000 mL of ether is usually sufficient.

10. A considerable amount of acid is present in the ether extracts, so vigorous gas evolution occurs during the sodium bicarbonate extraction. Caution must be exercised at this point.

11. The product is sufficiently pure for most purposes. A second distillation affords a colorless product (lit³ bp $88\text{--}90^{\circ}\text{C}$, 6 mm).

12. With many anilines used as precursors in this reaction, the sulfonyl chloride product is a solid and an alternate workup procedure is used. After the reaction is quenched with ice water, the solid product is filtered with suction and washed copiously with cold water. The crude product tends to occlude water and copper salts, which may be detrimental in later reactions. A good washing protocol involves rinsing the solid on the filter with water (2000 mL), then suspending the solid in cold water (1000 mL), stirring briskly, and filtering with suction. The latter process should be repeated three times. The final water wash should be only very

slightly yellow. After air drying the product can be recrystallized from an appropriate solvent.

3. Discussion

m-Trifluoromethylbenzenesulfonyl chloride has been prepared by treatment of *m*-trifluoromethylbenzenediazonium chloride with sulfur dioxide and hydrochloric acid⁴ and by conversion of benzotrifluoride to *m*-trifluoromethylbenzenesulfonic acid with oleum, followed by chlorination with phosphorus pentachloride.³ Derivatives of this compound, such as esters and amides, are quite useful in that they display reactivities similar to *p*- and *m*-nitrobenzenesulfonyl compounds but have greatly improved solubilities.

The described procedure essentially follows that described by Meerwein et al.² as modified slightly by Yale and Sowinski.⁴ This same method can be used for a great variety of substituted anilines with good results. As evident in Table I, good yields are obtained in most cases, and the reaction works better for anilines with electron-withdrawing substituents. The identical procedure has been used to prepare many other examples, such as *m*-F, *o*-F, 3,5-di- CF_3 .⁵ This method readily provides many unavailable arylsulfonyl chlorides, it is experimentally straightforward, and the products are isolated without complications.

TABLE I
CONVERSION OF ARYLAMINES TO ARYLSULFONYL CHLORIDES

Amine, $\text{XC}_6\text{H}_4\text{NH}_2$, $X =$	Yield (%) of $\text{XC}_6\text{H}_4\text{SO}_2\text{Cl}$
<i>m</i> - CF_3	72
<i>p</i> - NO_2	68
<i>m</i> - NO_2	86
<i>p</i> -Cl	90
<i>p</i> - CO_2CH_3	90
3,5-di- NO_2	81
<i>m</i> - CH_3	71
H	53
<i>p</i> - OCH_3	27

There are two general routes to arylsulfonyl chlorides. The first involves the conversion of an already sulfur-substituted aromatic compound to the sulfonyl chloride. Thus arylsulfonic acids or their alkali metal salts yield sulfonyl chlorides by treatment with a variety of chlorinating agents such as phosphorus pentachloride, thionyl chloride, phosgene, and chlorosulfonic acid. Alternatively, substituted thiophenols or aryl disulfides can be oxidized by chlorine-water to the sulfonyl chloride.⁶

The second route utilizes the introduction of the chlorosulfonyl substituent directly onto the aromatic nucleus. The reaction of substituted benzenes with chlorosulfonic acid gives good yields of arylsulfonyl chlorides; however, the aryl substituent dictates the position of attachment of the chlorosulfonyl function in this electrophilic aromatic substitution.⁷ The method described herein allows replacement of a diazotized amine function by the chlorosulfonyl group. The ready availability of substituted anilines makes this the method of choice for the preparation of arylsulfonyl chlorides.

Arylsulfonyl chlorides are pivotal precursors for the preparation of many diverse functional types including sulfonate esters,⁸ amides,⁴ sulfones,⁹ sulfinic acids,¹⁰ and others.¹¹ Furthermore, sulfonyl fluorides are best prepared from sulfonyl chlorides.¹² The sulfonyl fluorides have many uses, among which is their utilization as active site probes of chymotrypsin and other esterases.¹³ The trifluoromethyl group also plays valuable roles in medicinal chemistry.¹⁴

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Appendix

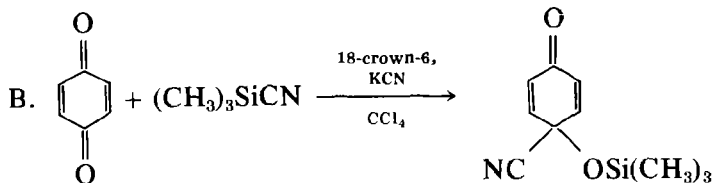
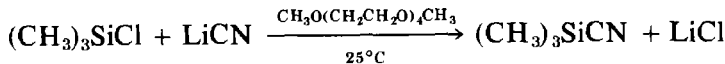
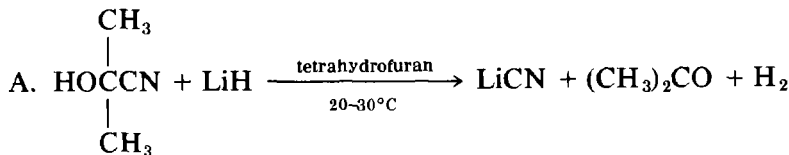
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Benzenesulfonyl chloride, *m*-(trifluoromethyl)- (8); Benzenesulfonyl chloride, 3-(trifluoromethyl)- (9); (777-44-6)

m-Aminobenzotrifluoride; *m*-Toluidine, α,α,α -trifluoro- (8); Benzenamine, 3-(trifluoromethyl)- (9); (98-16-8)

TRIMETHYLSILYL CYANIDE: CYANOSILYLATION OF *p*-BENZOQUINONE

(Silanecarbonitrile, trimethyl)



Submitted by TOM LIVINGHOUSE¹

Checked by TOD HOLLER, KEVIN J. CARLIN,
and G. BUCHI

1. Procedure

Caution! Trimethylsilyl cyanide is very toxic. All reactions in this sequence should be carried out in a hood.

A. Trimethylsilyl cyanide. A 1-L, round-bottomed flask equipped with a magnetic stirrer, nitrogen inlet, and a 60-mL addition funnel is charged with 5.0 g (0.624 mol) of lithium hydride (Note 1) and 500 mL of anhydrous tetrahydrofuran (Note 2). The stirred suspension is cooled in an ice bath and 42.6 g of acetone cyanohydrin (45.7 mL, 0.501 mol) (Note 3) is added dropwise over 15 min. After the addition is complete, the ice bath is removed and the mixture stirred for 2 hr at room temperature (Note 4). The magnetic stirring bar is removed and the solvent evaporated as completely as possible on a rotary evaporator. The white lithium cyanide is then dried in vacuo for 3 hr (Notes 5 and 6). The lithium cyanide is freed from the sides of the flask and broken up with a spatula (Note 7). A 250-mL, round-bottomed flask equipped with an ice bath, magnetic stirrer, thermometer, and nitrogen inlet is charged with 54.32 g (63.46 mL, 0.500 mol) of trimethylchlorosilane (Note 8) and 100 mL of bis[2-(2-methoxyethoxy)ethyl] ether (Note 9). The lithium cyanide is added to this stirred solution over 15 min through Gooch tubing (Note 10). After the addition is complete, the ice bath is removed and the milky suspension stirred overnight at room temperature. The Gooch tubing and thermometer are then removed from the reaction flask and a stillhead equipped for downward vacuum distillation is attached. A 100-mL, round-bottomed flask immersed halfway in an acetone-dry ice slush bath (Note 11) is employed as the receiver. The volatile compounds are distilled under a pressure of 50 mm (bp 25–55°C) by heating the contents of the pot using an oil bath (Note 12). The distillate is carefully redistilled through a well-insulated 15-cm column packed with glass helices under an inert atmosphere. A 25–40 mL forerun (bp 66–113°C), consisting primarily of tetrahydrofuran and hexamethyldisiloxane, is first collected. The second fraction, containing 29–41 g (59–82%) of trimethylsilyl cyanide (bp 114–117°C), $n_D^{25} 1.3902$ (Note 13), then distills. A purity of ca. 97% was established by GC analysis (Notes 14 and 15); the product is suitable for synthetic use without further purification.

B. Cyanosilylation of p-Benzoquinone. A 100-mL, round-bottomed flask equipped with a magnetic stirrer, West condenser, and

a nitrogen inlet is charged with 6.30 g (58.2 mmol) of *p*-benzoquinone (Note 16), 10 mL of dry carbon tetrachloride, and 8 mL (63.03 mmol) of trimethylsilyl cyanide. The stirred suspension is heated to a gentle reflux by means of a heat gun to dissolve all the *p*-benzoquinone. It is then allowed to cool slowly until the crystallization of the *p*-benzoquinone starts (Note 17), at which time 5 mg of the 1 : 1 complex between potassium cyanide and 18-crown-6 (Note 18) is added through the top of the condenser. An immediate vigorous reflux sets in and continues for 1–2 min (Note 19). The stirred reaction mixture is permitted to cool slowly to room temperature, whereupon the condenser is removed and 3 g of Florisil (Note 20) is added. After stirring for an additional 15 min, 10 mL of dry carbon tetrachloride is added. The suspension is then filtered and the filter cake leached with three 5-mL portions of carbon tetrachloride. The solvent is evaporated from the filtrate as completely as possible on a rotary evaporator, at which point crystallization of the residue usually begins (Note 21). The last traces of solvent and trimethylsilyl cyanide are then removed in vacuo over 20 hr at 50 μ to afford 12.0–12.2 g of crude product. The trimethylsilyl cyanohydrin is recrystallized by dissolving the crude material in 25 mL of hot *n*-hexane and allowing the resulting solution to cool slowly to room temperature (Note 22). After collection by filtration the product is rinsed with two 5-mL portions of hexane and air-dried to yield 7.54–9.77 g (63%–81%) of white to buff-colored needles, mp 65–67°C (Notes 23 and 24).

2. Notes

1. Commercial lithium hydride (Alfa Products, Ventron Corporation) was used.

2. Commercial tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.

3. Commercial acetone cyanohydrin (Aldrich Chemical Company, Inc.) was used without further purification.

4. A vigorous evolution of hydrogen gas occurs during the addition of the acetone cyanohydrin. Hydrogen evolution virtually ceases after stirring at room temperature for 2 hr.

5. It is essential to exclude atmospheric moisture as much as possible during this operation.

6. A small quantity of tetrahydrofuran remains complexed in the solid lithium cyanide and is separated later in the preparation.

7. This operation must be performed rapidly to avoid water absorption by the hygroscopic lithium cyanide.

8. Commercial trimethylchlorosilane (Silar Laboratories, Inc.) was distilled from calcium hydride immediately before use.

9. Commercial bis[2-(2-methoxyethoxy)ethyl] ether, "tetraglyme" (Eastman Organic Chemicals), was dried over Linde 4A molecular sieves for 24 hr before use.

10. The internal temperature is maintained at or below 35°C during this operation by periodic cooling with an ice bath.

11. Trimethylsilyl cyanide solidifies in the receiver during the course of the distillation. It is absolutely necessary that the receiver be immersed no more than halfway in the slush bath. Further immersion may cause the product to solidify in the end of the condenser. This necessitates cessation of the distillation to unclog the apparatus.

12. The temperature of the oil bath is raised from 25°C to 110°C over 45 min and then maintained at the upper temperature until no more product distills.

13. The product exhibits the following properties: ^1H NMR (CCl_4 with CHCl_3 internal standard) δ : 0.4 (s, $\text{Si}(\text{CH}_3)_3$); IR (neat) cm^{-1} : 2200 ($-\text{CN}$).

14. The GC analysis was performed on an 8-ft column packed with 5% Ov-17 on Anachrome ABS.

15. Trimethylsilyl cyanide hydrolyzes rapidly in moist air and is best stored under an inert atmosphere.

16. Commercial *p*-benzoquinone (Matheson, Coleman, and Bell, Inc.) was recrystallized from 95% ethanol before use.

17. The initiation of crystallization indicates the optimum reaction temperature for the catalyzed cyanosilylation of *p*-benzoquinone. The use of higher temperatures results in excessive darkening of the product and a decrease in yield.

18. The 1:1 complex is conveniently prepared by dissolving 0.652 g (10 mmol) of pulverized potassium cyanide and 2.640 g (10 mmol) of commercial 18-crown-6 (Aldrich Chemical Company, Inc.) in 45 mL of anhydrous methanol by swirling and warming. The methanol is then evaporated at a rotary evaporator and the white complex dried in vacuo over night.

19. Extreme care must be taken during the addition of the catalyst. The addition of too much catalyst or the use of higher reaction temperatures may result in the reaction mixture boiling over.

20. Florisil obtained from Matheson, Coleman, and Bell, Inc. was used.

21. Crystallization of the residue may also be induced by the addition of a seed crystal or scratching with a glass rod.

22. In some instances addition of a seed crystal during cooling is necessary.

23. *p*-Benzoquinone monotrimethylsilyl cyanohydrin darkens on prolonged exposure to light and air. It is best stored under nitrogen in the dark.

24. An analytically pure sample, mp 67–67.5°C, may be obtained by a second recrystallization from cyclohexane: ^1H NMR (CCl_4) δ : 6.83 (d, 1, $J = 10$ Hz, $\text{C}=\text{CH}$), 6.30 (d, 1, $J = 10$ Hz, $\text{C}=\text{CH}$), 0.30 (s, 9, CH_3); IR (CCl_4) cm^{-1} : 1678 ($\text{C}=\text{O}$), 1252, 845 ($\text{Si}-\text{CH}_3$).

3. Discussion

Trimethylsilyl cyanide is a useful reagent for the preparation of β -amino alcohols,² α -amino nitriles,³ and α -trimethylsiloxyacrylonitriles⁴ from the corresponding ketones, imines, and ketenes. The reagent adds rapidly to the carbonyl of aldehydes at 25°C,² and the resulting adducts have proven useful precursors for the preparation of carbonyl anion synthons.⁵ Enones give exclusively the products derived from 1,2-addition.²

Trimethylsilyl cyanide has been prepared in modest yield by the action of hexamethyldisilazane on hydrogen cyanide⁶ and the reaction of silver cyanide with trimethylchlorosilane.^{6,7} It has been prepared in good yield by the treatment of preformed lithium cyanide (from LiH and HCN) with trimethylchlorosilane in ether.⁷ The procedure described here not only affords trimethylsilyl cyanide in good yield, but also avoids the use of hydrogen cyanide and the need for Schlenk ware.

Table I illustrates the cyanosilylation of several representative ketones and aldehydes.

TABLE I
CYANOSILYLATION OF KETONES AND ALDEHYDES

Substrate	Silylcyanohydrin	Yield (%)	Reference
Benzophenone	(78) ^a	98	2
Crotonaldehyde	(88) ^a	98	2
Furfural		99	2
Cyclooctanone		94	7
Cyclododecanone		94	7
Camphor		>95 ^b	7
α -Tetralone		>95 ^b	7
3-Methyl-3-penten-2-one		91	7

^aNo catalyst employed; zinc iodide catalyst used in all other cases.

^bYield determined by GLC analysis.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Lithium hydride (8,9); (7580-67-8)

Acetone cyanohydrin: Lactonitrile, 2-methyl- (8); Propanenitrile, 2-hydroxy-2-methyl- (9); (75-86-5)

Lithium cyanide (8,9); (2408-36-8)

Silane, chlorotrimethyl- (8,9); (75-77-4)

Bis[2-(2-methoxyethoxy)ethyl] ether: Tetraglyme: 2,5,8,11,14-Pentaoxapentadecane (8,9); (143-24-8)

Trimethylsilyl cyanide: Silanecarbonitrile, trimethyl- (8,9); (7677-24-9)

p-Benzoquinone (8); 2,5-Cyclohexadiene-1,4-dione (9); (106-51-4)
18-Crown-6: 1,4,7,10,13,16-Hexaoxacyclooctadecane (8,9); (17455-13-9)

p-Benzoquinone monotrimethylsilyl cyanohydrin: 2,5-Cyclohexadiene-1-carbonitrile, 4-oxo-1-(trimethylsiloxy)- (8); 2,5-Cyclohexadiene-1-carbonitrile, 4-oxo-1-[(trimethylsilyl)oxy]- (9); (40861-57-2)

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This index comprises the names of contributors to Volume 60 only. For authors to previous volumes, see the cumulative indices in Volume 59, which covers Volumes 55 through 59, and Volume 54, which covers Volumes 50 through 54, and either the indices in Collective Volumes I through V or the single volume entitled *Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

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This index comprises subject matter for Volume 60 only. For subjects in previous volumes, see the cumulative indices in Volume 59, which covers Volumes 55 through 59, and Volume 54, which covers Volumes 50 through 54, and either the indices in Collective Volumes I through V or the single volume entitled *Organic Syntheses, Collective Volumes I, II, III, IV, V, Cumulative Indices*, edited by R. L. Shriner and R. H. Shriner.

The index lists the names of compounds in two forms. The first is the name used commonly in procedure. The second is the systematic name according to Chemical Abstracts nomenclature, accompanied by its registry number in brackets. Also included are general terms for classes of compounds, types of reactions, special apparatus, and unfamiliar methods.

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ORGANIC SYNTHESSES

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AN ANNUAL PUBLICATION OF SATISFACTORY
METHODS FOR THE PREPARATION
OF ORGANIC CHEMICALS

VOLUME 60

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